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PUBIC AND ISCHIAL NECROSIS FOLLOWING CYSTOSTOMY AND PROSTATECTOMY (OSTEITIS PUBIS)*

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IN 1923, the French urologists, Legueu and Rochet,[29] described a rare destructive disease of the pubis following cystotomy and prostatectomy. This was apparently due to extension of pelvic cellulitis from about the bladder and in the retropubic space through the obturator canals and into the origins of the adductors of the thighs. This disease resulted in septicemia, a development absent in the classical description by Beer[7,8] one year later and fortunately not characteristic of the lesion he named "osteitis pubis." It is benign and self limited and, although never fatal, may be the cause of severe and prolonged discomfort and disability. Moreover, since 1946, for no apparent reason, it has been reported with much greater frequency. Thus, it will bear serious consideration almost thirty years after the first description, for the riddle of origin and therapy is unanswered.

In recent years, it has been shown that osteitis pubis occurs rarely in several states (pyelonephritis[23] and ureterolithotomy[32] in women; resection of the rectum[1] and external trauma to the symphysis[25]); but it is almost entirely due to opening of the urinary bladder and/or prostatectomy. In order of incidence, suprapubic prostatectomy and retropubic prostatectomy have been the chief precursors; and to a much lesser extent, transurethral resection, cystectomy and perineal prostatectomy.[29]

Although this disease may be considered in the realm of urology, it is probably equally important that radiologists be thoroughly acquainted with it. In 1947, when Dr. Eldridge Eliason presented the authors with their first case, this lesion was a stranger to them and to the great majority of urologists and radiologists in Philadelphia. Since then, Klinefelter[24] and Leucutia[29] have made excellent reports for the radiologic literature, the latter counting 120 cases, including his own. To these will be added an experience with 9 cases, especially concerning the early diagnosis and roentgen therapy.

DIAGNOSIS

Symptoms and Signs. In the great ma-

* From the Department of Radiology, The Presbyterian Hospital in Philadelphia. Presented at the Fifty-second Annual Meeting, American Roentgen Ray Society, Washington, D. C., Sept. 25–28, 1951.

jority, the onset is from two to twelve weeks after prostatectomy, when the patient is at home enjoying his recovery from a serious illness. Mild and moderate cases may be seen uncommonly, but usually there is an abrupt and severe onset of pain in the pubic, perineal or inguinal areas, shortly spreading to several regions about the pubes and into the buttocks. The pain is constant, due in large part to spasm at the attachments of the recti and medial adductors of the thighs. Rotation and flexion of the trunk and thighs, walking, sitting, defecation and even urination prove painful; and the man takes to his bed in despair. There, he can only lie quietly, often in groaning misery.

The examiner will find no heat, redness or swelling, but a very marked tenderness over the symphysis or one pubic body primarily and, in a day or two, probably at the descending rami. The acute stage persists for a period of a few weeks to several months, varying widely. With great regularity the pain and tenderness migrate from the superior and inferior pubes to the ischial tuberosities, usually presenting in all three locations for several weeks at least, but gradually fading from the pubes and settling in the ischia for the latter period. The great tenderness, localized to the outline of the pubic bones, is highly characteristic of the early stage; and the radiologist can rely on making a certain diagnosis simply by examination of the pubes. This is the first step recommended and will serve to differentiate osteitis from other inflammations and metastatic malignancy before roentgenograms are positive. Attention to the physical signs and the history prevents confusion, as in the past, with epididymitis, seminal vesiculitis, cystitis and carcinoma.

General features of the disease may appear early: low to moderate fever; increased sedimentation rate; leukocytosis of 10,000 to 13,000; general malaise; anorexia; and, in severe attacks, mental depression, Thus, it can be understood that the disease suggests and is confused with other inflammatory or infectious lesions, among them classical osteomyelitis.

Roentgen Examination. This properly follows historical and physical evaluation. Within two weeks of onset a small lesion rarely may be demonstrated, but it usually requires two to four weeks for the first erosion to appear on roentgenograms made with the greatest care and attention to quality. The routine 14 by 17 inch film is not satisfactory. The early lesion demands the use of a small film, a long narrow cone, a 1 mm. focal spot and a suitable range of contrasts (preferably a high and a low).

Then, the small, isolated, cortical erosion will appear on one or both pubes, usually at symphysis or inferior rami, but uncommonly at the horizontal ramus (only 1 case appeared first in the ischia). This lesion progresses in about one week from a mere loss of the smooth cortical periphery to a more definite, irregular and ragged destruction extending over several inches, but never at this stage penetrating. Throughout the entire course, the striking features are those of a superficial bone destruction, confined to a depth of 1 to 5 mm., never transecting bone and rarely creating a sequestrum. *A study of the present series warrants adding two roentgenographic features to the classical picture: a bilaterality and symmetry of the lesions in pubes and ischia, appearing shortly after the first roentgen signs.* Within the period of acute lytic action, a generalized demineralization sometimes appears in the pubes and ischia.

The symphysial lesion is very characteristic. One of the first areas showing erosion, the nonossified space widens almost imperceptably within the first week of its disease and, then, more rapidly, until it may be two or three times normal width. The distortion can be quite irregular. A rare extension of the pubic lesion is that passing over the horizontal parts to the acetabulum. This occurred in Case IV of the present group, but was not severe. However, it is most alarming in view of the rare involvement of the hip joint by this disease (Case V). The portion of the pubis

forming the medial border of the obturator foramen has not been seen involved in the acute stage in this series, but apparently is implicated, since roentgenograms of the regenerative stage show spurs at these points. The natural progress of the symptoms is mirrored in the roentgen study: involvement first of the pubic corpora and/or inferior rami; increase of erosion in both or perhaps only in the rami; implication of the ischial tuberosities; a stage of regeneration.

The matter of sequestration is not agreed upon[29] because there is a difficult, and perhaps impossible, differentiation between severe osteitis and mild osteomyelitis.[3,10,13,34,36,46] Although no gross sequestrum has been shown on roentgenograms of the present series, Case III did produce small bone spicules from one of two perineal sinuses.

In two to twelve months the roentgenogram shows the stage of repair, new periosteal and cortical bone appearing with slight to severe distortion at the sites of former erosion. This repair progresses simultaneously with lysis in other areas, so that the two processes overlap. The regeneration of bone (in this series appearing more like irregular callus than smooth normal bone) may occur at descending rami or ischial tuberosities before reaching the symphysis; it may be small or great in amount; and the largest quantity and greatest distortion occur at the ischial tuberosities and the symphysis. The latter may heal with slight narrowing of the cartilage space, but usually (especially in the present cases) is obliterated by dense bone. The repair will cover widely varying periods, end stages not appearing before three to five years.

At this point it should be noted that the clinical state is almost always far ahead of the roentgen image. The patient is more sick in the acute stage and more well in the repair stage than his roentgenograms will indicate. The roentgenographic lag is similar to that found in osteomyelitis and malignant bone disease. Although the literature reveals symptom duration extending from one to thirty months, with the majority well in nine months, most of the discomfort is gone before much new bone appears to the radiologist. Hence, this therapist must take care to treat the patient, not the roentgenogram, stopping long before large amounts of callus have appeared. The regeneration of bone and addition of sizable spurs of periosteal callus is not attended by symptoms; nor is the presence of these spurs of any significance later.

COMPLICATION

In the available history of osteitis pubis 2 patients have had arthritis of one or both hips[15,42] after the usual disease had subsided. In the present report a third case is recorded (Case V). The immediate cause of extension of the lesion (it does seem to be an extension) is quite unknown. The final distressing result is well known: a destructive arthritis similar to pyogenic or rheumatoid disease, which abolishes the joint space and causes severe and permanent functional disability. This lesion probably is a pyogenic arthritis, although only in the case of Friedenberg has a specimen (pseudomonas pus) been recovered. The occurrence of hip disease lends greater strength to the theory of infection causing osteitis. Rapid response to treatment of the osteitis pubis does not obviate the occurrence of hip arthritis. Case V here was relieved of initial symptoms promptly. Treatment of this complication must be symptomatic until cases can be found early enough to confirm infection and treat it specifically. To treat the patient early is not easy. These men are prone to absent themselves; and both patient and physician may mistake the hip symptoms for those of pubic or ischial disease. If there is any question, the radiologist must be most alert in making roentgenograms.

ETIOLOGY AND PATHOLOGY

As in other diseases of unknown origin, the discussion of etiology and pathology is

very extensive. The theories may be summarized as follows:

1. Trauma to bone or periosteum.
2. Trauma to vessels, prostatic capsules and fascia.
3. Trauma to nerves.
4. Infection.
5. Trauma and infection.

1. Beer[7,8] was the first to suggest that trauma to the pubis by pressure of retractors and packing and avulsion of rectus and transversalis fibers was a very probable cause. Others[15,22,23,24] have agreed; and to reinforce this thought, there are 1 or 2 cases[24] in which external trauma to the symphysis has been a cause. Contrariwise, Wheeler[45] was unable to produce the lesion by pubic trauma and infection in rabbits; the disease does rarely follow perineal and transurethral prostatectomy; it has occurred after a simple pyelonephritis;[23] and, very important, it occurs in the work of skilled operators, more commonly in recent years, under surgical conditions considered optimum.

2. The argument for trauma to vessels, prostatic capsules and fascia[4,5,6,22] seems near the truth. Early in the work on the present report, Batson was consulted and expressed the belief that trauma to the prostatic venous plexus and, perhaps, to the small vessels serving the pubes and ischia was a causative factor. These veins and small arteries receive little attention; and yet are of such location and rich distribution that they may be strongly implicated and might bear study (Fig. 28 and 29). Due to the integration of the pubic, ischial and prostatic venous beds, a rupture of the prostatic capsule and plexus offers a reasonable cause for demineralization and cortical destruction, since an obstructive venous hyperemia has been provided by the amputation of the veins emerging from the pubes. Beach[6] described in great detail a pathogenesis involving injury to the prostatic capsules and septic spill. He says that, in the past, all operations (except perineal prostatectomy) were kept inside the true capsule, so as to avoid both septic spill and injury to the plexus. In transvesical enucleation, he indicates that the point of adherence at the pubes is sometimes torn; in transurethral resection the capsule is prone to injury, especially at the sides; and with retropubic operation the true and false capsules are purposely opened from the front. Some[21] of the urologists have abandoned the retropubic method; although Millin *et al.*[33] have accomplished 723 such prostatectomies with only 6 cases of osteitis resulting. *The discussion of trauma to the soft parts seems of the greatest importance, for it may stimulate and direct a search into the role played by the several types of modern operations.*

3. A third kind of trauma may be that to the nerves of the retropubic area. Very little, if anything, is known about this. Wheeler[45] offered a trophic disorder, Sudeck's atrophy, as a probable etiology. It is difficult to attribute the whole disease to this. The onset is rather early; infection is so prominent in numerous biopsies[6,15,18,22,35,36,38,42] that an aseptic necrosis hardly can be defended; and Sudeck's disease does not cause fever, leukocytosis, or irregular cortical erosion. However, this subject should not be dismissed without reference to the reports on erosive lesions of the pelvis and femora and soft tissue calcifications of these regions occurring in cases of paraplegia.[20,43,44] One biopsy revealed findings much like those in osteitis pubis.

4. Infection probably is the most favored[6,22,23,28] of all causal agents. Beach[6] believes that a septic spill occurs into the tissues about the prostate and is confined by inadequate drainage; that the infection cannot go caudad or posteriorly and must proceed anteriorly; that it collects in a niche overlying the pubic nutrient foramina (Fig. 29) and thence proceeds to the obturator foramina and ischia. He believes that the retropubic collection is attested by two facts: no case has been reported following uncomplicated perineal prostatectomy, because accumulation cannot occur

with dependent drainage; and, in the female, cases are rare because the peculiar structure creates little opportunity for accumulation (3 or 4 women have been reported).

Batson[4,5] and Harrison[19] do not support the spill theory. Batson suggests that only slight pressure may force infection through veins and lymphatics to numerous foci. This seems highly probable. Harrison points to the occurrence of the lesion in women and in patients having no operation; and to his observation that osteitis victims usually show more of poor wound healing or breakdown than the average. Whatever may be the mechanism, it seems that infection does exist and spread.

Connected to the thoughts above are those of Millin *et al.*,[33] who believe that modern surgery may create such rapid closure of wounds that complete drainage of all types of organisms, especially the resistant, is not possible. So, these urologists have abandoned the routine use of penicillin at operation, hoping that there will be no confinement of resistant organisms in the wound. Modern medicine is indeed too much with us! In favor of this theory is the apparent increase of the disease since 1946, when early ambulation had become popular surgical practice. The increase may be only apparent, since, in these times, prostatectomy seems required of nearly all men as a passport to senility.

The differentiation of osteitis pubis from classical osteomyelitis appears clear to Leucutia[29] and Dinan,[13] but seems difficult to us. Several reports,[3,10,13,28,34,36,41] some labeled osteomyelitis and some not, deal with a disease which seems to differ only in degree from osteitis. The cellulitis, pubic destruction, abscess formation and toxemia of Legueu and Rochet[28] may be yesterday's serious infection which is limited by today's methods to a benign osteitis. The biopsies of others[6,15,18,22,35,36,38,42] and of our Case IV show a bone disease variously presenting debris, pus, periosteal, cortical and sometimes marrow destruction and formation of sinuses, as in our Case III. The only factor lacking to make such lesions typical osteomyelitis is sequestration. Even this occurs in minute size (Case III). Of the cases presently reported, Cases VI and IX may be considered mild (always ambulant); Case V mild in the pubes, but virulent in extending to the hip (all without sequestrum or sinus); Case III a severe type, with two sinuses and small sequestra; and Case VIII a serious lesion causing deep penetration of the pubis, without sinus or sequestrum. We believe these cases are one disease.

Whatever the label, there is ample evidence to substantiate infection as a causative factor, even though probably not the only one. The clinical picture of mild systemic disease (leukocytosis, fever, increased sedimentation rate and malaise); the roentgen image of a bone destruction progressive from pubes to ischia; and the biopsies, all serve to demonstrate infection. Nine biopsies have been found reported. The tenth is from our Case IV:

1. Peirson
   Chronic inflammation of soft tissue.
2. Riaboff (autopsy)
   No signs of inflammation, but a decrease in the number and thickness of bone lamellae. Bone architecture was readily recognized. Uniform loss of bone substance, not merely a depletion of mineral salts.
3. Silver
   a. Symphysis: nonspecific acute inflammation of cartilage and fibrous tissue.
   b. Tuber ischii: chronic osteomyelitis. Pus—*B. coli.*
4. Muschat
   Subacute osteomyelitis of the pubis. Pus—*B. proteus* and *Staph. aur. hem.*
5. Goldstein and Rubin
   Loose cellular connective tissue in marrow, infiltrated by polymorphonuclears, lymphocytes and a few histiocytes. Irregular margins to some bone trabeculae.
6. Kirz
   a. Soft tissue abscess: pyogenic granulation tissue plus fat showing chronic inflammation and fibrosis; a few spicules of bone present. Pus—*B. pyocyaneus.*
   b. Spongy bone; mild chronic inflammation of fatty marrow.
7. Beach (2 cases)
   A panosteitis, with periosteal implication, pus, rough bone and granulation tissue.

8. Friedenberg
   Hip: pseudomonas pus.
9. Lame and Chang
   Granuloma overlying symphysis: granulation tissue containing areas of destructive suppuration. Sparse scattering of dead bone spicules, some of which lie in pools of pus, others having evoked a foreign body giant cell reaction.
   Diagnosis—chronic suppurative osteitis and periostitis.

The etiology is probably composite: a neurovascular disturbance with infection, for some reason confined below the limits of classical ostomyelitis.

TREATMENT

Earlier efforts were confined to bed rest, sedation and analgesics, later complemented by diathermy, supportive slings and plaster casting (especially where orthopedists were concerned). In recent years, antibiotics, vitamin B, roentgen irradiation and ACTH enter the field prominently, all in search of a more constantly effective agent.

Bed rest is always indicated in the severe cases.

Diathermy is reported useless.

Supportive and fixation appliances are valued highly by some authors[6,15,35] and seem to be rational. They have not been used in the present series.

Antibiotics, especially the later ones, would be expected to show great value, but, as far as known, have not produced one good result. They have been observed under thorough trials in this present group.

Vitamin B proved of value in the hands of two groups,[1,25] at least, but the total of patients is not great and further work is needed. Cases VIII and IX of this report suggest that a partial relief may be expected from vitamin B and C.

Roentgen Therapy. First tried by Goldstein and Rubin,[18] it has appeared in three other reports,[1,25,29] the best documented being that of Leucutia.[29] Goldstein and Rubin employed extremely large amounts, as would apply in carcinoma. On personal inquiry, they agree that smaller dosages may be advisable. In some of the cases of Leucutia[29] large quantities were applied, apparently in the belief that malignant disease existed; but, in retrospect, this author recommends small divided doses, stopping before bone repair is complete. The work done on the present group unquestionably indicates the validity of this principle.

Due entirely to the great fortune of having Case I referred to us already diagnosed, all of the lesions in this series were interpreted as osteitis; and an immediate decision was made in favor of irradiation by small, frequent doses. Although the principle was violated, subsequent work confirms the initial belief that more than a few hundred roentgens to one portal is not helpful; and that irradiation should be halted before attainment of complete freedom from symptoms. If therapy is continued past a moderate total (as in Cases III and IV), the patient may cease improving; and eventual cure recedes into the distance as dosage adds up to large sums. This phenomenon may be due to persistent bone inflammation, unresponsive to therapy. It is reasonable to expect that application of such large amounts as to cause formation of much collagen, serious vascular necrosis and fibrous scar would not aid a lesion inherently characterized by such changes. Thus, the therapy plan in this series (with 2 notable exceptions) has the been same as for common inflammations, such as tendinitis, carbuncle and cellulitis. If there has been an error in underdosage, it is due to the use of small portals, which omit some involved muscles and tendons.

As in rheumatoid spondylitis and degenerative arthritis, we believe that the beneficial influence of roentgen therapy stems from soft tissue, not bone, effect. There is an undeniable relief of spasm and pain, but usually not a lasting one; and no certain evidence of a change in the character of the bones as a sequel to irradiation.

Another plan needing investigation is that of simultaneous treatment of all areas known to be typically involved at any time

in the illness. In the present series, portals have been chosen as pain and tenderness dictate, perhaps with the hope that other portals would not be needed. This may be a mistake. The simultaneous therapy on superior and inferior pubes and ischia might have benefited Cases II, VI, VII, VIII and IX, especially if soft tissue infection is a precursor to bone disease and can be halted by roentgen treatment. No one yet knows whether small quantities of radiation would benefit the early stage of hip arthritis. This phase of the disease is too rare (±2 per cent) to prompt a recommendation for routine prophylaxis but we would favor the use of a modest dose in the early acute stage. The therapy of choice in the chronic disease is orthopedic surgery.

Cortisone and ACTH. With the knowledge that osteitis is impermanent and in the belief that it is an alarm reaction to a serious insult, a trial of cortisone was planned. The expectation was prevention of extravasation of serum and cells and alteration of acute inflammation to one of chronicity, thus shortening the course and perhaps preventing much bone involvement. Inquiry among our colleagues elicited no data on this application of the drug. Cortisone was used as the initial treatment in Case VII, starting one month after onset and continuing for sixteen days. The relief from pain was most remarkable, but lasted only thirteen days. The drug may have been curtailed too soon; but, at any rate, the therapy was diverted to irradiation and no other case received cortisone. Conclusions are hardly warranted.

ACTH received glowing praise from three workers. Leberman[27] treated a woman and observed rapid relief. Dyer[14] treated a man for only six days and cured him. Dean[12] managed 3 patients and reports prompt and striking benefit, as opposed to earlier results with irradiation.

For these reasons, our Cases VIII and IX received ACTH rather than cortisone, despite the temptation to continue investigation of the latter. Case VIII had no benefit whatever from nine days of treatment and refused a second trial. Irradiation was substituted and caused prompt and striking partial relief. Case IX received simultaneous therapy by ACTH, vitamins B and C and irradiation. Therefore, conclusions on the effect of ACTH are difficult, although it appeared valuable. This was a very mild case and was expected to respond well. With great regret, we are unable to confirm the excellent results reported; but hope that further trial may be possible.

Prophylaxis. Preventive therapy has received some thought[6,33] recently. Beach believes that the older partial prostatectomies should be resumed, since the modern radical procedures are probably causative. He points to the tight closure of the bladder, the routine use of antibiotics, the possible lack of repair of the prostatic capsule and the creation of excessive bleeding in current practice. Harrison assures us that there is no difference in his operative technique of the pre- and post-osteitis eras. Although we are not able to judge urologic surgery, there may be several indications to suggest a review of surgical practice:

a. The disease follows urologic operations almost entirely.

b. It occurs in patients expected otherwise to recover without incident, not usually in poor risks. Of 9 cases, 1 had a poor kidney; 1 was only a medium risk undergoing multiple operations; and the rest would be classified as good to excellent risks, including 2 young men.

c. It is apparently more common in latter years.

d. It responds hesitantly and irregularly to various methods; and may be found never to yield to any agent of active therapy. Hence, the need for prevention.

CASE REPORTS

A summary appears in Table 1. Detailed accounts are available, but omitted here to conserve space.

CASE DISCUSSION

Case 1. This was the first case of osteitis pubis known by the existing medical staff to

TABLE I

	Operation and Date	First Symptoms and Date	Bones Involved First Roentgenograms	Interval Onset to Roentgen Therapy	Drug and Roentgen Therapy (r in air) Elapsed Time	Response to Therapy	Symptom Duration	
							Total	After irradiation
Case I C	Suprapubic cystotomy and ureterotomy 2/25/47	Pain in groins then buttocks 4/20/47 (8 weeks)	Pubes and ischia 5/28/47	6.5 mo.	200 r symphysis 500 r post ischia 18 days	Prompt and marked. Nearly asymptomatic in 17 days	7.5 mo.	1 mo
Case II H	Suprapubic cystotomy and prostatectomy 8/ 6/47	Pain in ischial tuberosities and medial thighs 9/20/47 (6 weeks)	Ischia 11/ 8/47	2 mo.	600 r each ischium 7 days	Prompt and marked in 5 days. Very slow thereafter	6 mo.	4 mo.
Case III P	Suprapubic cystotomy and prostatectomy 11/ 5/47	Pain in pubes and buttocks 11/27/47 (3 weeks)	Pubes 12/22/47	8 mo.	850 r symphysis 68 days 1,450 r each ischium 134 days 1,500 r desc. rami 252 days	Questionable Slow—poor	20 mo.	12 mo.
Case IV B	Suprapubic cystotomy and prostatectomy 7/14/48	Pain in medial thighs 7/31/48 (2 weeks)	Pubes and ischia 10/30/48	3.5 mo.	650 r symphysis 18 days 1,000 r each ischium 157 days 1,400 r desc. rami 88 days	Prompt—painless in 2½ weeks, but recurrence—very slow thereafter	11 mo.	7.4 mo.
Case V M	Suprapubic cystotomy and prostatectomy 7/30/48	Pain in groins and buttocks 8/24/48 (4 weeks)	Pubes 9/11/48	3 weeks	550 r symphysis 550 r each ischium 29 days 300 r symphysis 4 days	Prompt and marked in 1st wk. No pain in 33 days. Hip later showed permanent arthritis	Pubes and ischia 8 wk. Hip arthritis permanent	5 wk.
Case VI S	Suprapubic cystotomy and prostatectomy 6/21/50	Pain in rt. desc. pubis ramus 7/ 5/50 (2 weeks)	1 pubis 8/14/50	1.3 mo.	600 r symphysis 700 r desc. rami 53 days	Prompt at initial site—second site involved—then gradual response	5.5 mo.	4.2 mo.
Case VII B	Suprapubic prostatectomy; spermatocele; hernia repair 12/ 6/50	Pain in desc. pubic ramus 1/ 9/51 (5 weeks)	1 pubis 2/ 1/51	7 weeks	Cortisone—16 days 400 and 600 r pubes 500 r each tuberosity 38 days	Roentgen therapy fair at first—out of bed 10 days; slow thereafter	Pain at 4 mo. No more follow-up possible	
Case VIII K	Suprapubic cystotomy and prostatectomy; fulgeration bladder cancer 3/ 7/51	Pain in pubes 4/14/51 (5 weeks)	Pubes 4/19/51	20 days	ACTH—9 days Vitamin B and C—2.5 mo. 500 r sup. pubes 500 r, 300 r } inf. pubes 700 r, 450 r } isch. tuberosities 3 mo.	ACTH useless. Vitamins and roentgen therapy: relief marked in 4 days; slow thereafter	5.5 mo.	4.8 mo.
Case IX C	Suprapubic cystotomy and prostatectomy 4/ 4/51	Pain in groins 5/ 5/51 (1 mo.)	Pubes 5/15/51	10 days	ACTH—13 days Vitamin B and C—2.5 mo. 500 r sup. pubes 500 r symph. and rami 450 r inf. rami 300 r each tuberosity 51 days	Prompt and marked relief in 4 days; then slow thereafter (combined therapy)	9 mo.	8.7 mo.

Fig. 1. Case 1. Roentgenogram loaned by Dr. Bernard P. Widmann. Five weeks from onset of pain in pubis and ischium; three months from cystotomy and right ureterotomy. Tender mass over each ischial tuberosity. Cortical erosion of symphysis and descending pubic rami and into tuberosities.

have entered Presbyterian Hospital; and certainly the first case ever seen by the authors. Roentgen therapy was entered upon with great caution and with a decision to employ as little as would relieve the patient. Hence, the use of small divided doses, totalling 200 roentgens (in air) and 500 r (in air) to the two portals respectively. It was at this time decided not to use the dosage running into several thousands of roentgens described by other workers,[18] since damage to the bone was feared.

This man offered something of a control case, since he had suffered for six and a half months before reaching roentgen treatment. Although he may have been due to recover, it is striking

Fig. 2. Case 1. Roentgenogram loaned by Dr. Bernard P. Widmann. Ten weeks from onset. Stage of repair starting. Bony spurs visible. Pain and tenderness persist.

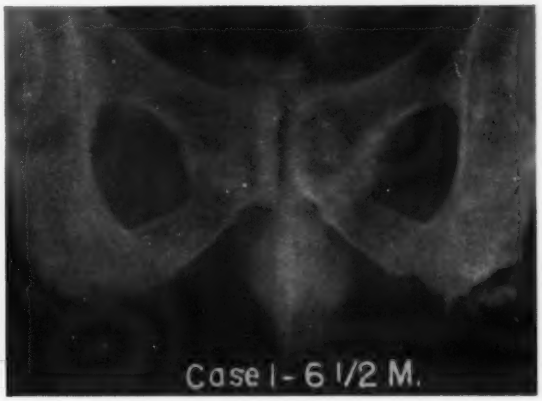

Fig. 3. Case 1. Six and one-half months. Ischial masses incised and roentgen therapy started. Pain and tenderness abolished in one month by irradiation. Bony overgrowth increasing.

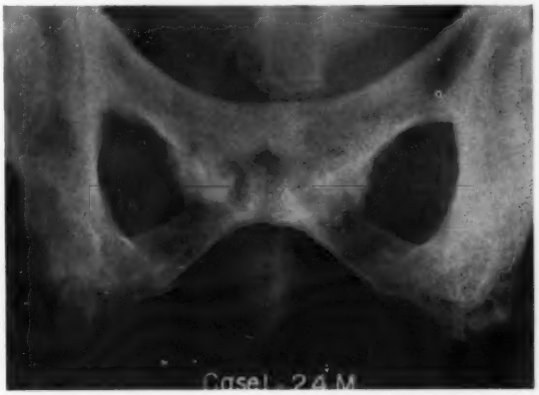

Fig. 4. Case 1. Twenty-four months. Solidification of symphysis.

Fig. 5. Case 1. Four years. End stage. Asymptomatic three and one-half years.

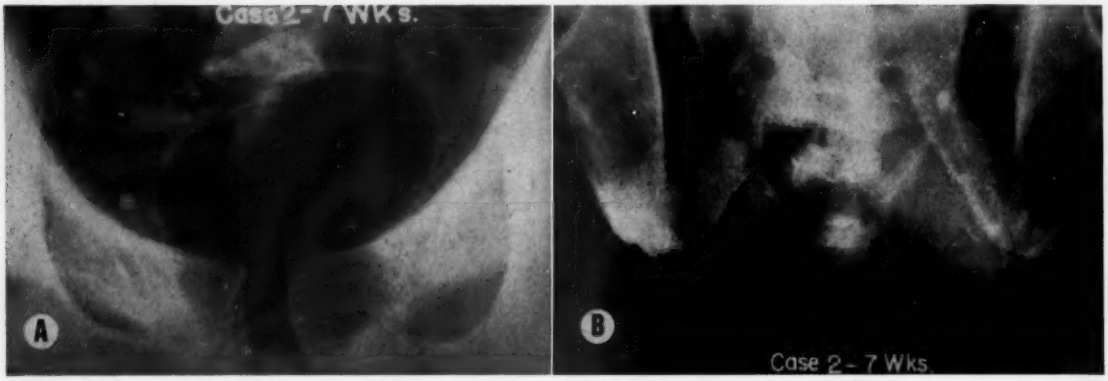

FIG. 6. (*A*) and (*B*) Case II. Seven weeks from onset of pain and tenderness over both ischial tuberosities and pain in medial parts of the thighs as far as the knees. Note cortical erosion of the ischial tuberosities but no lesion at symphysis (rare finding).

coincidence that he was relieved immediately after two days of irradiation and cured in one month.

It is interesting to learn that incision over the tender ischial masses, but not down onto the bone, disclosed no suppuration.

Case II. Variation is frequent in this disease, exemplified by this man demonstrating an isolated ischial tuberosity erosion when first examined completely at seven weeks from onset of pain. The disease had avoided his pubes (which are almost always involved first), certainly a rare incident; and not until a delayed follow-up examination was it proved that the lesion had struck there also. It was probably the pubic disease chiefly that caused the four month illness following irradiation to the ischia; and it might have been wise to treat the pubes early before they were roentgenographically positive and before the patient disappeared. However, in this man as in Case I, there was an unmistakable prompt response to roentgen treatment.

Case III. This case was one of the most baffling and discouraging. Having spent eight months in a confused and thoroughly unfortunate experience, he came to radiation treatment with a severe chronic disease attended by sinus formation. It is such a lesion that some workers[13,29,34,41] believe is osteomyelitis rather than osteitis. Although the disease never threatened life, fever, pus, sequestration and sinuses occurred; but the patient had the same pain, tenderness and roentgen signs as are characteristic of osteitis. It is very difficult to

FIG. 7. Case II. Fourteen and one-half months from onset. Asymptomatic since six months. Close follow-up refused, so that progress of destruction is not recorded before healing stage. Symphysis solidifying. End stage at thirty-eight months.

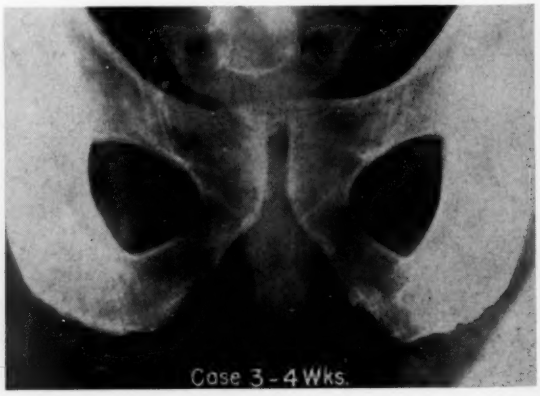

FIG. 8. Case III. Four weeks after onset of pain and tenderness in right groin and symphysis. Ambulant with difficulty. Early cortical erosion shown in both descending rami, but not at symphysis. Lesion difficult to see on original film.

Fig. 9. Case III. Nine and one-half months. Large bony spurs present. Roentgen therapy started one and one-half months earlier. *Ischial sinuses* had developed before and after irradiation instituted but general discomfort much less at this date.

differentiate the two according to the definitions in the literature. Roentgen therapy was given for eight and a half months in the hope of relieving the stubborn symptoms by small divided dosage, but that proved nearly useless. The quantity used is not recommended. An absolute cure date cannot be given, although this man was almost well twenty and a half months after onset.

Case IV. This patient came to our observation at a relatively late date ($3\frac{1}{2}$ months after onset), with an interesting lesion extending to the acetabulum. Due to a diagnosis elsewhere of metastatic tumor in the pubes, a biopsy of prevesical tissue was secured (our only one). From this, a

Fig. 10. Case III. Forty months. Nearly end stage roentgenologically. Appears very well with no tenderness, but reports ache in abdomen, pubes and testes and bearing down sensation in rectum. No cause demonstrated.

Fig. 11. Case IV. Three and one-half months after onset. Suffering pain in pelvic girdle on almost any motion, with tenderness over entire pubes laterally to the pelvic walls and down to the tuberosities of the ischia. Erosive lesion well seen extending to the medial aspect of acetabula and into descending rami. Feces obscures symphysis. Biopsy. Irradiation started.

purulent bone destruction was demonstrated. The only therapy was irradiation, which yielded prompt partial relief, but was continued in three courses for five and a half months, due to persistent pain and limitation of function. As is so often true, the irradiation was not the complete solution, although the dosage reached 1,400 r (in air) to one portal ($5\frac{1}{2}$ months). Such an amount has proved of little or no use (see Case III).

Case V. In some respects this patient was the most gratifying in the series. Within five weeks he was transformed by roentgen therapy from

Fig. 12. Case IV. Nine months. Chronic stage clinically and roentgenologically. Slight tenderness at tuberosities. Irradiation for five and one-half months; dosage relatively large.

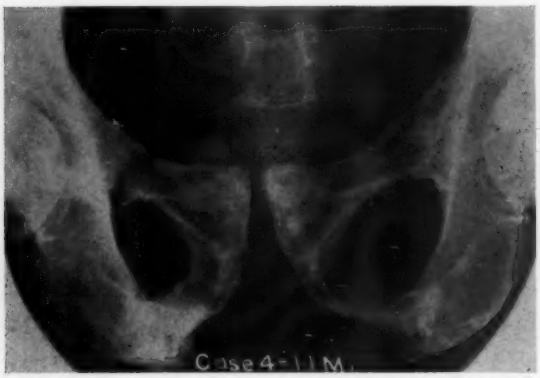

FIG. 13. Case IV. Eleven months. Well. Eburnation of bones. End stage seen at thirty-three months but omitted here.

an extremely sick man physically and emotionally to one able to walk cheerfully out of the hospital. Control therapy with antibiotics had preceded. No recurrence of pubic and ischial pain developed, but the right hip became involved several weeks after therapy was stopped. Unfortunately, the patient spent the next year removed from Philadelphia, so that an accurate first hand account of the acute hip affection is not available; nor were roentgenograms of the early disease made. However, it was apparently the same destructive process as seen first by Silver[42] and recently by Friedenberg[15] shortly after the experience above.

No other cases are known and no record exists of roentgen therapy for the hips. Silver described no treatment. Friedenberg successfully

FIG. 14. Case V. Three weeks after onset of pelvic pain; five weeks after prostatectomy. Early but definite erosion of superior border of symphysis and descending rami. Bed ridden and unable to move pelvis or lower limbs without severe pain. Note normal hip joints. Roentgen therapy caused prompt relief; went home ambulant at eight weeks.

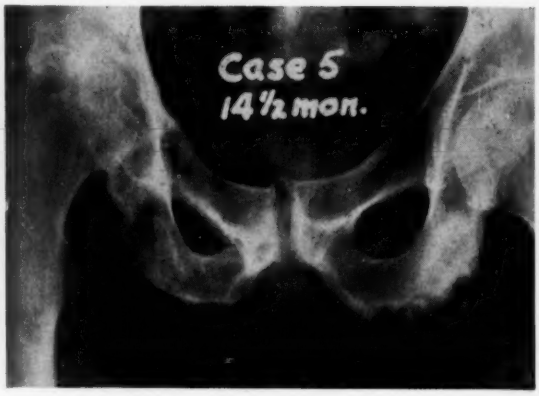

FIG. 15. Case V. Fourteen and one-half months. Pubes and ischia appear well healed. Right hip suffering destructive arthritis apparently secondary to pubic osteitis. Severe pain and limitation of motion in hip. No roentgen treatment offered for hip.

FIG. 16. Case V. Twenty-seven months. No recurrence of pubic or ischial symptoms. Bones repaired. Hip progressive but now chronic clinically.

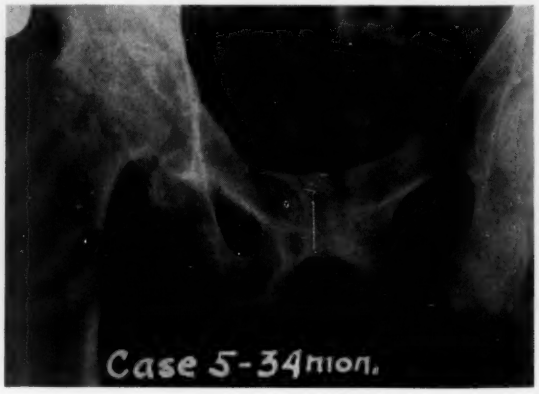

FIG. 17. Case V. Thirty-four months. End stage of pubic and ischial disease. Hip less painful but permanently damaged.

Fig. 18. Case vi. Six weeks after onset of pain in right pubis and right thigh and limitation of motion in both thighs. Now tender at right side of symphysis and right descending ramus. Roentgenogram shows early erosion at symphysis and right descending ramus. Irradiation started.

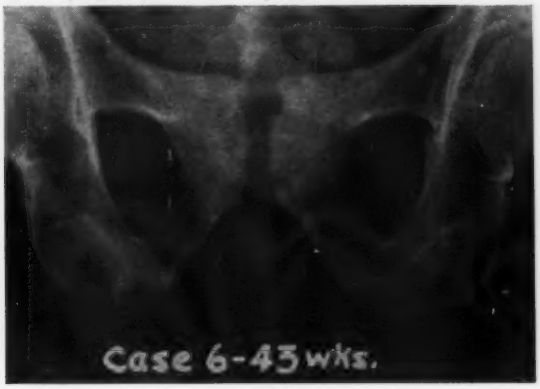

Fig. 20. Case vi. Forty-three weeks. Clinical cure at five and one-half months. Note maximum roentgen destruction at symphysis now, four and one-half months after last symptom. Eburnation expected later, but the hypertrophic character is missing so far.

used a bone graft to fix the joint, probably the therapy of choice. This was recommended by us for Case v, but not accepted. *It is important to record this disease as another rare cause of arthritis of the hip;* and to plead the case for early immobilization. Noteworthy is the fact that a pubic and ischial lesion may heal promptly and be followed by the serious hip involvement.

Case vi. This man presented a mild case of osteitis following recovery from a ruptured appendix and a suprapubic prostatectomy. If the infected peritoneum is considered a factor in etiology, greater severity of osteitis should be expected. He was treated by irradiation alone and received prompt but incomplete relief by this means. Clinical cure occurred at five and a half months after onset. It will be noted that, to restrict the total amount of irradiation, it was first directed only to the area that was most symptomatic, *viz.*, the right pubis; and that this method did not prevent the characteristic spread of the lesion to the left side. The natural course of the disease demonstrates involvement of bones in this order; symphysis and/or superior pubes; descending rami; and lastly ischial tuberosities (see Case ii).

Case vii. This man had multiple urinary and

Fig. 19. Case vi. Fourteen weeks. Last irradiation one week before. Clinically much improved; only slight tenderness on left ramus and a tightness in the girdle. Further destruction at symphysis; right inferior ramus healing; left ramus slightly eroded.

Fig. 21. Case vii. Three weeks after onset of pain in left, then the right, inferior pubic ramus. Now tender only on right. Very small cortical erosion seen at the right descending ramus, probably not visible in reproduction. This is roentgen stage important to diagnose.

FIG. 22. Case VII. Four and one-half weeks. Five days after cortisone started. Striking improvement clinically, but lesion increasing at superior symphysis and both inferior rami by roentgenogram. Example of clinical and roentgen difference.

FIG. 24. Case VIII. Twenty-one days (?). ACTH for nine days without success. Marked advance of lesion. Left inferior ramus shows one of deepest erosions seen by authors. Marked demineralization noted. Irradiation started.

genital lesions and underwent extensive surgical operation complicated by infected herniorrhaphy and hydrocele wounds. It is the first case in which complete reliance was not placed on irradiation. Cortisone was urged by us, since irradiation has not been a complete therapy; because of a few reports of success with ACTH;[12,14,27] but chiefly because this case was thought to be most appropriate for such a drug: an early stage of self-limited disease, probably due to vascular damage and infection, in which it would be highly desirable to delimit the alarm reaction at an early date, so that cell elaboration and granulation tissue formation would be minimized and the stage of repair, as well as that of activity, be shortened. There has been shown an occasional increase of vascular wall permeability with the use of cortisone. This risk was calculated and may be an explanation of an increase in severity of the symptoms toward the end of the dosage. On the other hand, the dosage itself may have been too short, since the man lost his gain when the amount of cortisone was decreased; although a duration of sixteen days would seem a proper choice of trial time. If the disease osteitis were common, frequent and varied trials could be had on patients exhibiting the variation in severity usual in the affection. Conclusions on one patient are not trustworthy.

FIG. 23. Case VIII. Three days (?) after onset of severe pain in pubes and muscles of groins. Now bed ridden with pain and tenderness over entire pubes. Early lesion seen at right symphysis and both inferior rami, more advanced than history would indicate.

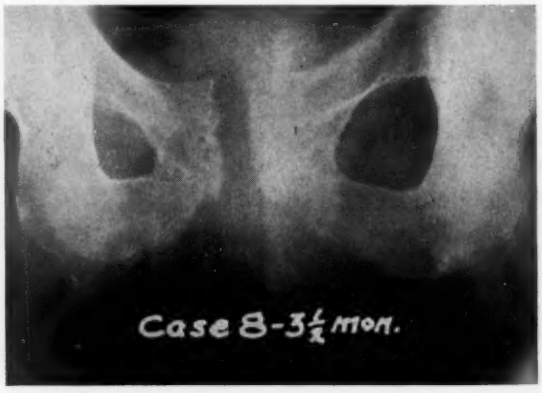

FIG. 25. Case VIII. Three and one-half months. Walking part of day during work. Pain on stair climbing, tender only at right inferior ramus. Recalcification and repair of inferior rami noted, but tuberosities of ischia involved (last, as usual). Cure at five and one-half months.

In summary, this man had a fairly early stage of osteitis treated with initial success by cortisone; the benefit being lost promptly when the dosage was cut. He then had irradiation attended by partial and slow response, which was more than usually disappointing, since the prelude of cortisone was expected to enhance the good effect of the roentgen therapy. The follow-up is very unsatisfactory.

Case VIII. This patient had a small carcinoma of the bladder, benign prostatic hypertrophy and multiple small abscesses of the prostate. A pneumonitis disturbed the convalescence. Al-

Fig. 26. Case IX. Twelve days after onset. Very slight erosion of symphysis only, although pain at symphysis and inferior rami. ACTH and irradiation started.

though there was no indication of spread of the cancer, the prostatic abscess may have influenced the severity of the osteitis, which was seen to penetrate the bone more deeply than in other cases. In the hope that a better result than with cortisone could be had, ACTH was used for nine days. There was no benefit, so that irradiation was employed, with a resultant sharp relief, not maintained. The addition of large doses of vitamins B and C, recommended by several authors,[25,30] was attended by another striking relief; but, again, not held completely. However, with the presentation of each of the last two media, appreciable progress was made, although the symptoms ebbed slowly, until, at a date three and a half months from onset, the man was almost well. A severe sciatica intervened at this point, yet he recovered from both diseases five and a half months after the osteitis began. Considering the complication and the patient's temperament, the result is

Fig. 27. Case IX. Five weeks. Further erosion at symphysis and new lesions seen in inferior rami. Great clinical improvement, not maintained completely. Irradiation directed to tuberosities for pain one week hence. Cure at nine months. Later stages omitted here.

considered rather satisfactory. The credit may be attributed to irradiation and vitamins, but further trial of ACTH seems indicated.

Case IX. As in Case VI, this man came to treatment with a mild disease. Simultaneous therapy with ACTH, irradiation and vitamins was chosen. Relief of symptoms was prompt and partial, followed by an irregular persistence of mild pain and tenderness for three months, when a peptic ulcer lay hold of him. He had not recovered from osteitis until the nine month inspection, a real disappointment in view of the mild onset. The benefit seen was not so clear-cut as that found in some cases (I, II, V and VI) receiving only irradiation. ACTH was used for thirteen days; roentgen therapy for fifty-one

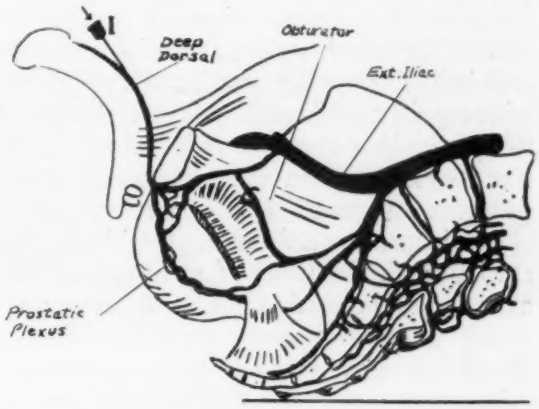

Fig. 28. From Batson. Sagittal section diagram of venous system of pelvis. Note rich prostatic plexus adjacent to pubis and ischium.

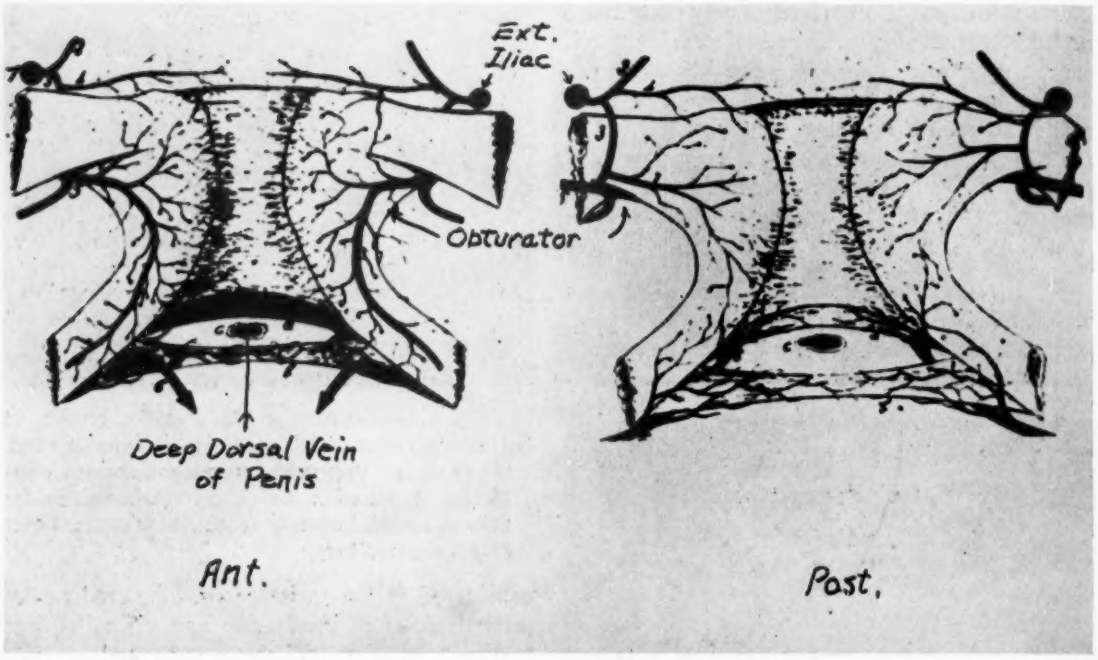

FIG. 29. From Ribet, suggested by Batson. Anterior and posterior aspects of pubes showing numerous nutrient vessels and available penetration of bones. Trauma to these vessels or transmission of infection by them may be important in etiology of osteitis.

days; and vitamins B and C for two and a half months. These methods cannot be condemned, but a need for therapeutic experiment on many more patients is evident.

RESULTS

It remains only to summarize the results of roentgen therapy of these 9 cases. The usual effect (in 8 of 9 cases) has been prompt, partial relief within a few days, followed by a period of weeks or several months in which symptoms of decreasing and irregular quality persist. Although all of the pain and disability is not abolished in the early days, the relief obtained is most welcome; and the method of small frequent roentgen dosage is recommended.

An inspection of Table 1 will supply statistics on duration of symptoms. The average total duration, for the 8 cases completed (disregarding the hip lesion), is 8.3 months. The hip arthritis well may be considered a separate and distinct addition to the pubic disease. A useful comparison with most of the published data is nearly impossible. In an analysis of 114 cases, the duration of symptoms was not stated for 53. Of the remaining 61, the average duration was 9.7 months and the mean about 9 months. Duration after therapy is unknown. This type of comparison does not reveal the valuable result obtained in partial relief of symptoms. Statistics on the symptoms and bone lesions of this disease are incomplete and sometimes unreliable. Partly as a consequence, the clinical and roentgen criteria applied are highly variable; and the inherent variability of the disease creates more confusion. Coincident with the interest in this disease expected among radiologists, there should appear detailed reporting of roentgen therapy and accurate appraisal of results.

In the present state of our knowledge, osteitis pubis has little susceptibility to specific agents, but, rather, demands symptomatic treatment. One cannot be ashamed of a partial relief. Undeniably, a rather prompt complete relief does occur; we have seen it transpire twice in this series in periods of a few weeks; but it is neither routine nor common.

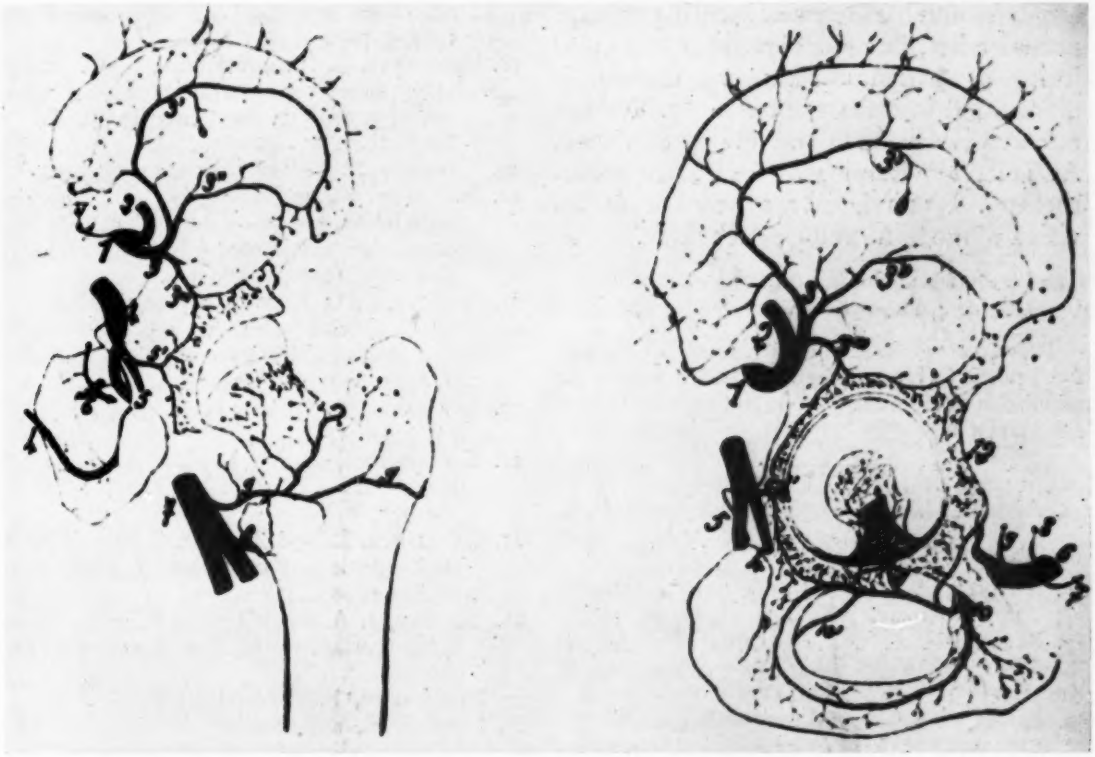

Fig. 30. From Ribet, suggested by Batson. Posterior and lateral aspects of hip region showing vascular supply and relation to pubis and ischium. Transmission of infection from pubis to hip offers probable explanation of rare complication.

SUMMARY

Osteitis pubis is a benign, self-limited disease, probably closely related to osteomyelitis. It occurs almost entirely after cystostomy and/or prostatectomy. It is a disabling illness, which has been recognized more frequently in recent years. The study of early diagnosis and treatment should arouse serious radiologic interest. Nine cases are here added to the reports which record well over 100 others.

The diagnosis is discussed in detail: pain and tenderness in the pubes, occurring one to twelve weeks after urologic operation, often causing severe disability and systemic signs of infection; after two or three additional weeks, characteristic bilateral cortical erosion of the pubes, progressing later into the ischia. Early diagnosis is best made by careful attention to the history and physical signs and then by accurate roentgenologic methods. Complications consist of very uncommon sinus formation and a very rare destructive arthritis of the hip, of which the third case is reported here.

The etiology and pathology are obscure. This report suggests that three factors are concerned: trauma to nerves; trauma to vessels and connective tissue; and infection. The discussion of trauma seems important, for it may stimulate a search into the part played by modern urologic operations. Nearly all of the 10 instances (1 reported here) of histopathologic examination reveal bone destruction suggesting infectious origin.

Treatment past and present are reviewed. All the present cases received roentgen therapy by a method of small fractionated doses. Large amounts are not recommended. One patient received cortisone and 2 patients ACTH and vitamins in addition to irradiation. Roentgen ther-

apy is a valuable means of securing prompt partial relief, but not cure, in a large majority of patients. Recovery usually is more rapid in cases treated early. Further research is needed in therapy by cortisone, ACTH and vitamins as well as in radiotherapy. Prophylaxis may consist of revision of modern urologic technique.

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The authors are indebted to Dr. Joseph C. Birdsall, Dr. Francis G. Harrison and Dr. Henry Sangree for permission to report their cases and for their cooperation and aid.

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DISCUSSION

DR. LLOYD G. LEWIS, Washington, D. C. My experience with osteitis pubis has, fortunately, been limited to one case. Dr. Lame has given you a splendid résumé of his very excellent paper, which includes everything that needs to be said about this disease.

I agree that it is an infectious process. It seems significant to me that patients who had osteitis pubis following suprapubic surgery, whether cystotomy, suprapubic prostatectomy, retropubic prostatectomy or ureterolithotomy, had their earliest involvement on the superior surface of the symphysis, whereas osteitis pubis following perineal prostatectomy has involved the inferior surface of the symphysis. Although my experience with suprapubic and perineal prostatectomy had been extensive, I had never seen osteitis pubis until I began to do retropubic prostatectomy.

Urologists stayed out of the space of Retzius with great fear and trepidation. Until Millin perfected the retropubic operation, we never exposed the prostate on the anterior surface if we could help it. What would be the advantage of getting into this bloody area? Patients following suprapubic prostatectomy have a great amount of postoperative pain, distention, require a great deal of sedation, whereas after retropubic prostatectomy, they have a minimum of postoperative discomfort. I have done 65 retropubic operations and have never used more than $\frac{1}{6}$ gr. of morphine postoperatively for pain.

I would like to report one case because of a few interesting details. I saw another in consultation at Walter Reed General Hospital, an almost identical situation.

My patient, sixty-three years of age, was admitted to Doctors' Hospital in Washington on November 11, 1947, with typical symptoms of prostatism due to enlargement of the lateral and middle lobes. The anterior commissure of the prostate was elongated to such a degree that I felt we could do the new operation with the greatest of ease. I had done one previously.

The operation was performed exactly according to the technique of Millin. I used packing on the sides of the prostate and, as you can see from Dr. Lame's pictures of the blood supply of the pubic area, those lateral packings could very well interfere with the blood supply to the symphysis, but they are very loosely placed to keep the fat out of the way.

Blood vessels were ligated on the surface of the prostate. An incision was made in a bloodless field, the prostate was enucleated with the greatest of ease, the capsule was sutured completely, his postoperative course for four days was uneventful. On the fourth day I removed his urethral catheter and he was unable to void. Immediately following catheterization he had a chill with a temperature of 103°F. The catheter was removed and from then on he voided perfectly.

It was noted on the fifth postoperative day that he had a small abscess in his rectus sheath which was opened and drained. He went home on the thirteenth day after operation, voiding well, feeling perfectly well. On December 8, twenty-six days after surgery, he developed typical symptoms of osteitis pubis: pain in the abdomen, tenderness over the pubis, bilateral adductor spasm and the usual disability. It is almost impossible for these patients to get out of bed.

Roentgenograms of the pelvis were reported as negative. However, we immediately began treatment for osteitis. Dr. McPeak administered from December 9 through December 12, 600 roentgens through a 15 by 15 cm. portal, using 220 kv. with a Thoraeus filter at 50 cm. distance from the anterior symphysis pubis.

There was very slight change in his clinical condition until December 26, at which time he could get around with some difficulty. Roentgen findings at that time indicated the typical lesion as Dr. Lame has shown you in his films.

I am very much interested in Dr. Lame's films. The two patients I have seen had their lesions limited to the symphysis pubis almost at the midline; there was no involvement along the pubic or ischiadic rami.

This patient received no penicillin. He did have some intravenous sodium sulfathiazole at the time of his chill. It has been thought by some that we attenuate organisms with inadequate dosages of penicillin, delaying the inflammatory reaction for three or four weeks. I am convinced that in my case, and in the one I saw in consultation, the infection was produced by an abscess in the rectus sheath which extended down to the periosteum of the symphysis pubis.

I have done sixty-three more operations through the same route, using exactly the same technique, with no further incidence of osteitis pubis; but following that incident, I have not put any sutures in the rectus sheath below the drains. The reason we are seeing more and more osteitis pubis is due to the fact that the urologist is impressed with the necessity of getting his patient out of the hospital in the shortest possible time. We have been using inadequate drainage; closing some wounds. I believe osteitis pubis can be prevented by adequate drainage of the space of Retzius.

DR. JACOB R. FREID, New York, N. Y. Necrosis of the pubic bone, as an occasional complication of suprapubic prostatectomy, was first described by Dr. Walter Beer about twenty years ago. Several years later I had occasion to present to the New York Roentgen Ray Society two cases of necrosis of the pubic bone successfully treated by roentgen therapy. These lesions are not common, but from time to time reports have appeared in the literature of successful treatment of these complications by radiation therapy.

Vol. 71, No. 2

NEPHROTOMOGRAPHY

A PRELIMINARY REPORT

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OPACIFICATION of the renal parenchyma as an aid in the differential diagnosis of renal and extrarenal lesions was recognized soon after the development of excretory urography. During excretory urography contrast visualization of the renal substance was noted not infrequently in patients with acute ureteral obstruction,[3,11,12] and the term nephrogram was used to designate this phenomenon. Realizing the diagnostic value of roentgenologic contrast visualization of the kidney parenchyma, Weens and Florence[9] used artificial measures to obstruct the ureter and thus obtain a nephrogram. The many practical disadvantages of such a procedure soon led to its abandonment. It was not until organic compounds of high iodine concentration and low toxicity were developed that practical methods of visualizing the renal parenchyma became available. At present the two effective methods of producing satisfactory nephrograms are transabdominal aortography[2] and the rapid intravenous injection of concentrated organic iodine solutions by the method developed by Robb and Steinberg[5] for angiocardiography. The former method has all the disadvantages of being an elaborate technique. The possibilities of the latter method for visualization of the renal parenchyma were recognized by Steinberg and Robb[6] in the course of their early studies. It was not until some time later, however, that Weens *et al.*[10] published the first report on intravenous nephrography. Subsequent observations were reported by Vesey, Dotter and Steinberg[7] and recently by Wall and Rose.[8] The latter investigators, using urokon sodium 70 per cent, a compound having a higher iodine concentration than other available organic iodine compounds and a low toxicity, obtained uniformly good opacification of the renal parenchyma in their cases. Satisfactory demonstration of the abdominal aorta and renal vessels was obtained on the first films in approximately 50 per cent of their cases. In addition, the excretory urograms closely paralleled the diagnostic quality of those secured by retrograde study.

Despite good opacification of functioning renal parenchyma by the intravenous technique, the clarity of the renal mass is compromised by the superimposition of intestinal contents and gas. Furthermore, small renal lesions embedded in the substance of the kidney might easily be missed on plain nephrography because of being enveloped by functioning parenchyma. These difficulties are not of major importance if the procedure is to be used mainly as a test of differential renal function. However, if, as it would seem to us, the most important contribution of the method permits recognition of areas of nonfunctioning or malfunctioning renal parenchyma as occurs in cysts and neoplasms, then any impediment to complete delineation of the renal parenchyma would be of paramount importance. A technique which eliminates the adulteration of the nephrogram by extraneous abdominal contents and in addition visualizes the midcoronal plane of the kidney should then permit precise study of renal morphology. Body section roentgenography combined with intravenous nephrography we feel accomplishes this aim. This conjoint technique we have called "nephrotomography." Its possibilities were recognized by Pendergrass[4] in his Carman Lecture of 1942 when

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he stated, "Body section roentgenograms of the kidneys after the injection of a contrast medium may reveal changes that cannot be seen in the conventional examination." The value of combining these techniques was also suggested by Weens and Florence[9] who, in discussing the opacified kidney shadow following artificial obstruction of the ureter, stated that in conjunction with laminagraphy they obtained satisfactory roentgenograms of the kidney in the lateral view.

The purpose of this paper is to describe the technique of the examination and to

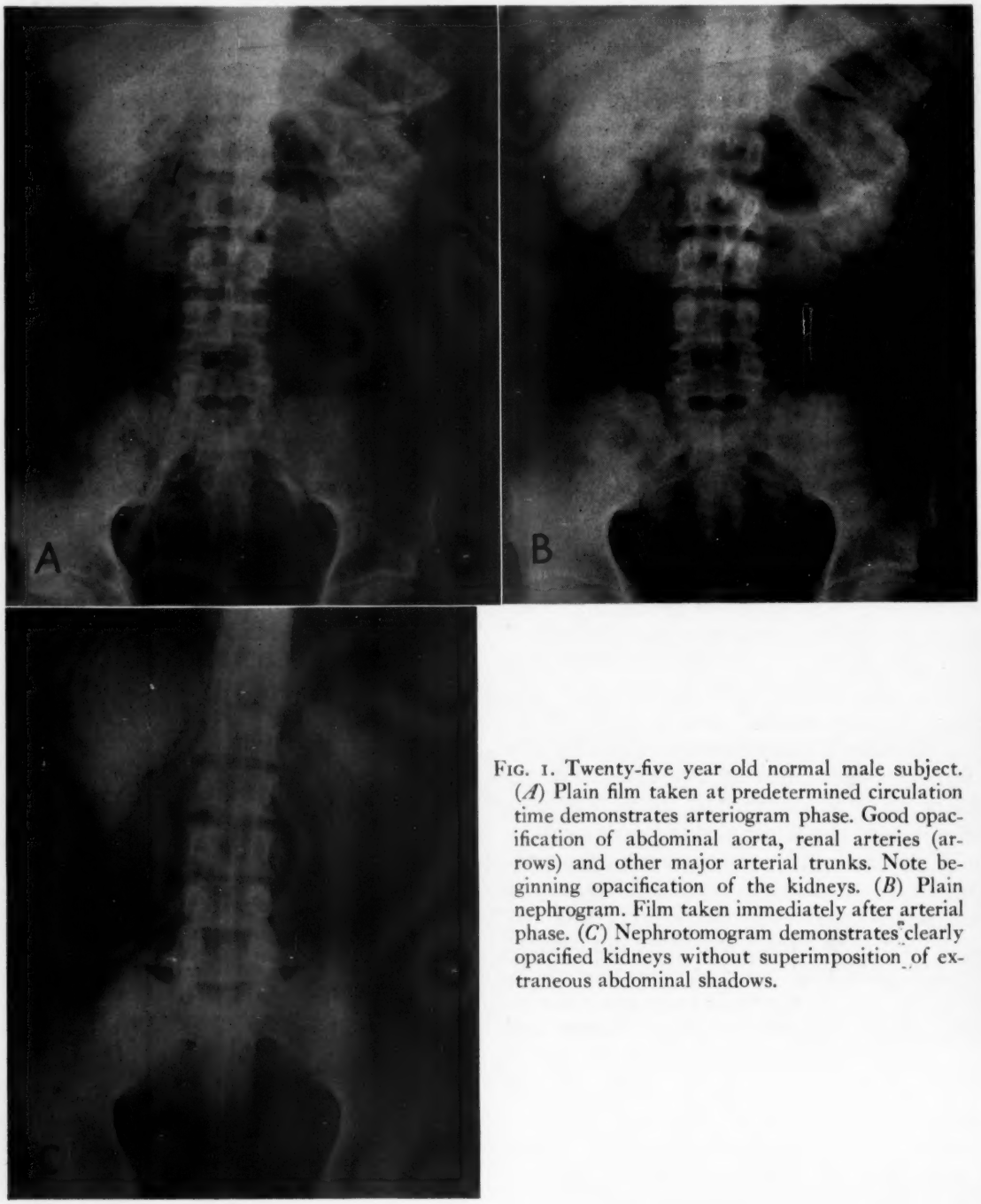

FIG. 1. Twenty-five year old normal male subject. (*A*) Plain film taken at predetermined circulation time demonstrates arteriogram phase. Good opacification of abdominal aorta, renal arteries (arrows) and other major arterial trunks. Note beginning opacification of the kidneys. (*B*) Plain nephrogram. Film taken immediately after arterial phase. (*C*) Nephrotomogram demonstrates clearly opacified kidneys without superimposition of extraneous abdominal shadows.

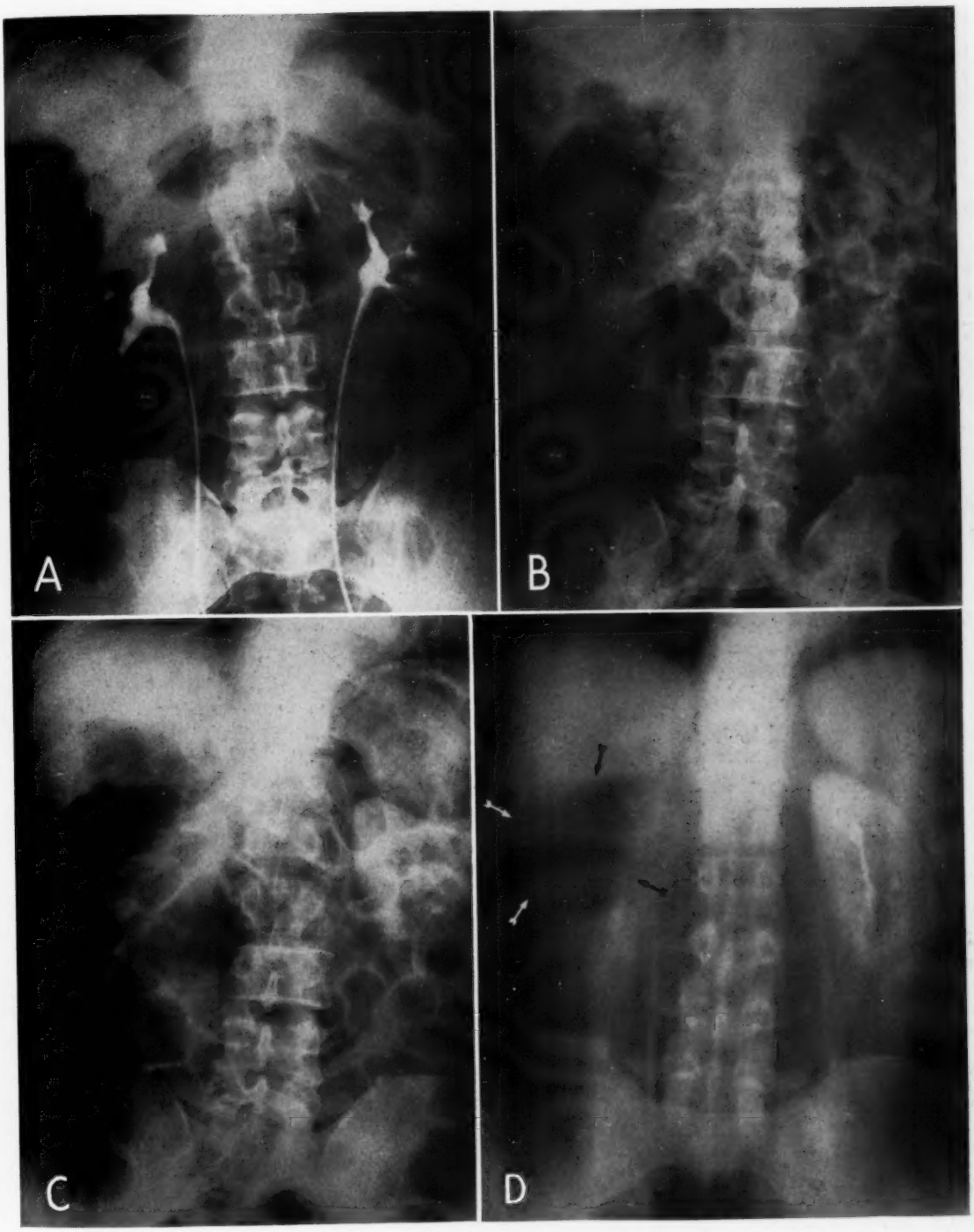

Fig. 2. (*See page 216 for legend*)

FIG. 2. Fifty-four year old male. Upper urinary tract investigated because of hypertension. (*A*) Retrograde pyelogram suggests presence of mass (cyst or neoplasm) in the upper pole of the right kidney. (*B*) Arteriogram phase revealed no abnormal vascular bed in the suspected area. (*C*) Nephrogram reveals opacification of both kidneys, but the right kidney is obscured by overlying bowel. (*D*) Nephrotomogram demonstrates a clear cut, rounded radiolucency in the upper pole of the right kidney representing a large cyst. (*E*) Plain film following percutaneous aspiration of cyst and injection of contrast medium. Fluid was clear and negative for neoplastic cells.

report our preliminary observations of the method.

TECHNIQUE

(1) The patient is positioned supine on a roentgenographic table equipped for tomograms.

(2) Preliminary plain films and tomograms are obtained to be used as control films and to check the roentgenographic technique.

(3) A 12 gauge Robb-Steinberg angiocardiographic needle is inserted into an antecubital vein.

(4) Arm-to-tongue decholin circulation time is determined, employing the same injection technique as for the contrast substance.

(5) Prior to the injection of the urokon it is advisable to rehearse the injection with the patient and warn of the sensations to be expected so that there will be no movement or breathing during the exposures. We feel that sensitivity testing is of little value. This opinion is based on a very extensive angiocardiographic experience in this department and the survey on angiocardiographic mortality conducted by Dotter and Jackson.[1]

(6) With the roentgen tube in mid-position, 50 cc. of urokon sodium 70 per cent is rapidly injected (in 1.5 to 2 seconds) into the abducted arm. A film is then exposed at the predetermined circulation time. The first roentgenogram will demonstrate the renal arteries. This is followed as rapidly as possible by a second film which secures the nephrogram. Immediately after the second exposure a tomogram is obtained (Fig. 1, *A*, *B* and *C*). The elapsed time between the first exposure and the completion of the tomogram should not exceed twenty-five seconds.

(7) After inspection of the films, a second injection may be considered necessary. A repeat circulation time is advisable before the second injection because we have found that the circulation time is delayed after the first injection, presumably due to an increase in the peripheral resistance. If this is not done, opacification of the abdominal aorta and renal vessels will not be secured.

RESULTS

The method to date has been used in 20 cases. Each case was selected because of a suspected renal lesion detected by routine urographic studies. In addition, two control examinations were carried out on normal subjects. One control was examined with multiple serial exposures by means of a Fairchild magazine. This demonstrated the time sequence of opacification. Maximum opacification of the aorta and renal arteries occurred at one-half second later than the decholin circulation time. The nephrogram began at one and one-half seconds after the circulation time, and reached a maximum at five to nine seconds after the circulation time, and faded at thirty-two seconds.

In 12 of the 20 cases, the abdominal aorta and renal arterial system were satisfactorily

Fig. 3. (*See page 218 for legend*)

FIG. 3. Fifty-three year old female with recurrent carcinoma of bladder. (*A*) Retrograde pyelograms reveal distortion of right calyceal structures suggesting cyst or neoplasm. (*B*) Arteriogram demonstrates the vessels are slightly distorted in the region of the mass. (*C*) Nephrogram shows a poorly defined radiolucency in the area of the lesion. The collecting system is filled because of a previous injection. (*D*) Nephrotomogram reveals the lesion of the right kidney to be a cyst. In addition, a cyst of the left kidney is demonstrated. This was not suspected on the routine urogram or plain nephrogram. (*E*) Plain film following aspiration of cyst of the left kidney and replacement with air (arrow). Aspirate negative for neoplastic cells. The cyst of the right kidney was proved by surgery.

demonstrated. In several of our earlier examinations no attempt was made to obtain an arteriogram or the time of the exposure was incorrect. Good nephrograms were obtained in 12 cases and good nephrotomograms in 15 cases. Even in those cases where the examination was considered not entirely satisfactory useful information was gained. The failure to secure adequate studies in several cases was due to (1) technical factors, (2) inability of the patient to cooperate, and (3) a nonfunctioning kidney.

In 6 cases a renal lesion was demonstrated on the nephrotomogram when the plain nephrogram did not reveal a lesion (Fig. 2). The nephrotomogram in 1 case demonstrated a cyst in the opposite kidney which had not been suspected or demonstrated on the conventional excretory urogram or plain nephrogram (Fig. 3).

The nephrotomogram was more diagnostic than the nephrogram and more clearly suggested the character of the lesion in 8 cases (Fig. 4).

One case in which renal pathology was suspected in the conventional urograms was shown to have a normal kidney on nephrotomography.

Of the 20 cases, there were 13 instances of renal masses in which routine urography had not differentiated between cyst and neoplasm. By means of nephrotomography we felt we were able to make a definite diagnosis of cyst in 5 cases and an equivocal diagnosis of cyst in 2 cases. The diagnosis in all of these cases was confirmed by surgery or aspiration. The diagnosis of neoplasm was made in 5 cases, all confirmed by surgery. In 2 of the 5 neoplasms, conventional urography suggested a small mass lesion in the kidney. An arteriogram was not secured in 1 case and in the other failed to clearly define a pathological blood supply. The nephrotomograms did not identify the character of the lesions. They did by our criteria, rule out cysts. The diagnosis of neoplasm in these 2 cases was made, therefore, on a basis of exclusion.

One case, in this group of renal masses, was interpreted as an extrarenal tumor. Surgery proved it to be a solitary cyst which arose from the surface of the kidney.

A few cases of suspected extrarenal masses were examined. One subject exhibited a compression and distortion of the upper pole of one kidney by what appeared to be an extrarenal mass. This was interpreted as an adrenal tumor, but surgery revealed only an enlarged spleen which was compressing the upper pole of the kidney. In another instance, nephrotomography demonstrated what appeared to be a mass

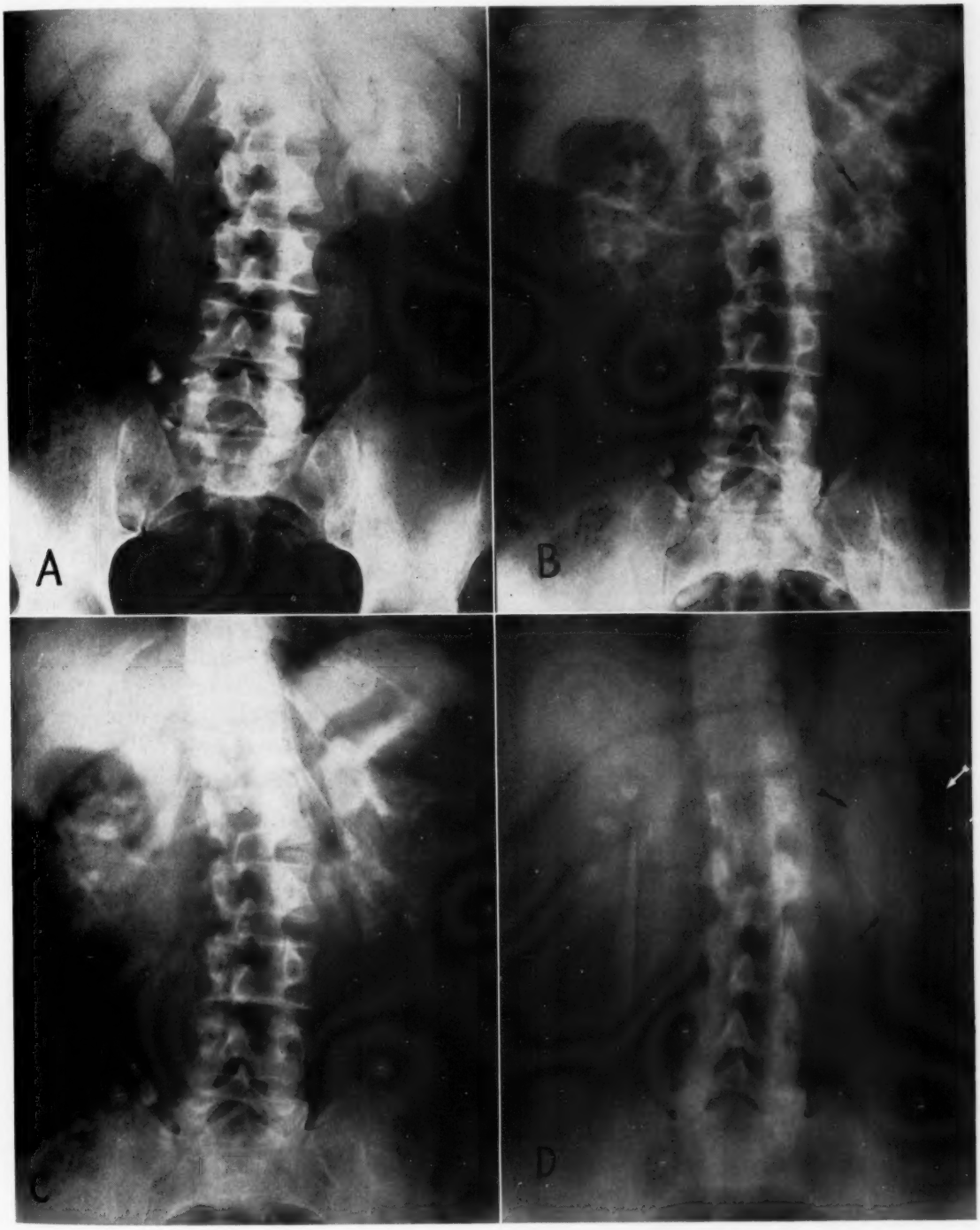

Fig. 4. (*See page 220 for legend*)

FIG. 4. Fifty-nine year old male with hypertension and left flank pain. (*A*) Intravenous urogram reveals large rounded mass in the upper pole of the left kidney with associated distortion of calyceal structures. (*B*) Arteriogram shows the vessels (arrow) in the region of the mass to be displaced inferiorly. (*C*) Nephrogram reveals lack of opacification of the mass. Definition poor due to overlying gas. (*D*) Nephrotomogram clearly demonstrates a large cyst of the upper pole of the left kidney. Artefact overlying right kidney. (*E*) Plain film showing aspiration of cyst and replacement with air. Cyst contents negative for neoplastic cells.

at the upper pole of the kidney. This was interpreted as a possible adrenal tumor, but surgery revealed only a slight hypertrophy of the adrenal which did not correspond to the density seen on the nephrotomogram. It is possible that a lobulated upper pole of the kidney was mistaken as the tumor in this instance.

In the small group of patients examined there have been no serious reactions or untoward side effects. The only effects noted have been a transient hot flush and occasional mild pain along the injected vein. This parallels our angiocardiographic experience with urokon sodium 70 per cent which, up to this writing, has been used in 574 patients receiving a total of 977 injections.

DISCUSSION

We have found that nephrotomography allows a better study of the renal morphology and in many cases gives a clear definition of renal pathology. One of the greatest difficulties we encountered with plain nephrograms was obscuration by overlying intestinal gas. This problem is eliminated in nephrotomograms because of the single plane section (Fig. 2, *C* and *D*).

The procedure is of greatest value in the differentiation of cysts from neoplasms. Cysts appear as sharply outlined, rounded, radiolucent areas which are delineated by opacified surrounding renal parenchyma (Fig. 5*C*). In the arteriogram phase of the examination there may be a distortion of the vascular pattern in the region of the cyst. Neoplasms have not exhibited the sharp, precise outlines that cysts have shown. They appear, moreover, to blend with the adjacent renal parenchyma. In contradistinction to cysts, neoplasms appear slightly opacified. The density of the mass, however, is not nearly as marked as normally functioning renal tissue. The arteriogram is of great value because it demonstrates a pathological vascular bed in the renal mass (Fig. 6). In most of our cases, we were able to differentiate between cysts and neoplasms with accuracy. In the cases where a differentiation could not definitely be made, technical factors were at fault.

The renal outline is very sharply delineated by nephrotomography. This should be of value in differentiating renal from extrarenal masses and in demonstrating congenital anomalies of the kidneys.

The procedure was attempted in one case of polycystic disease but successful films were not obtained because of poor renal function and lack of cooperation on the part of the patient. However, we feel that the method will prove to be of diagnostic value in this condition.

It is our intention to employ multiple

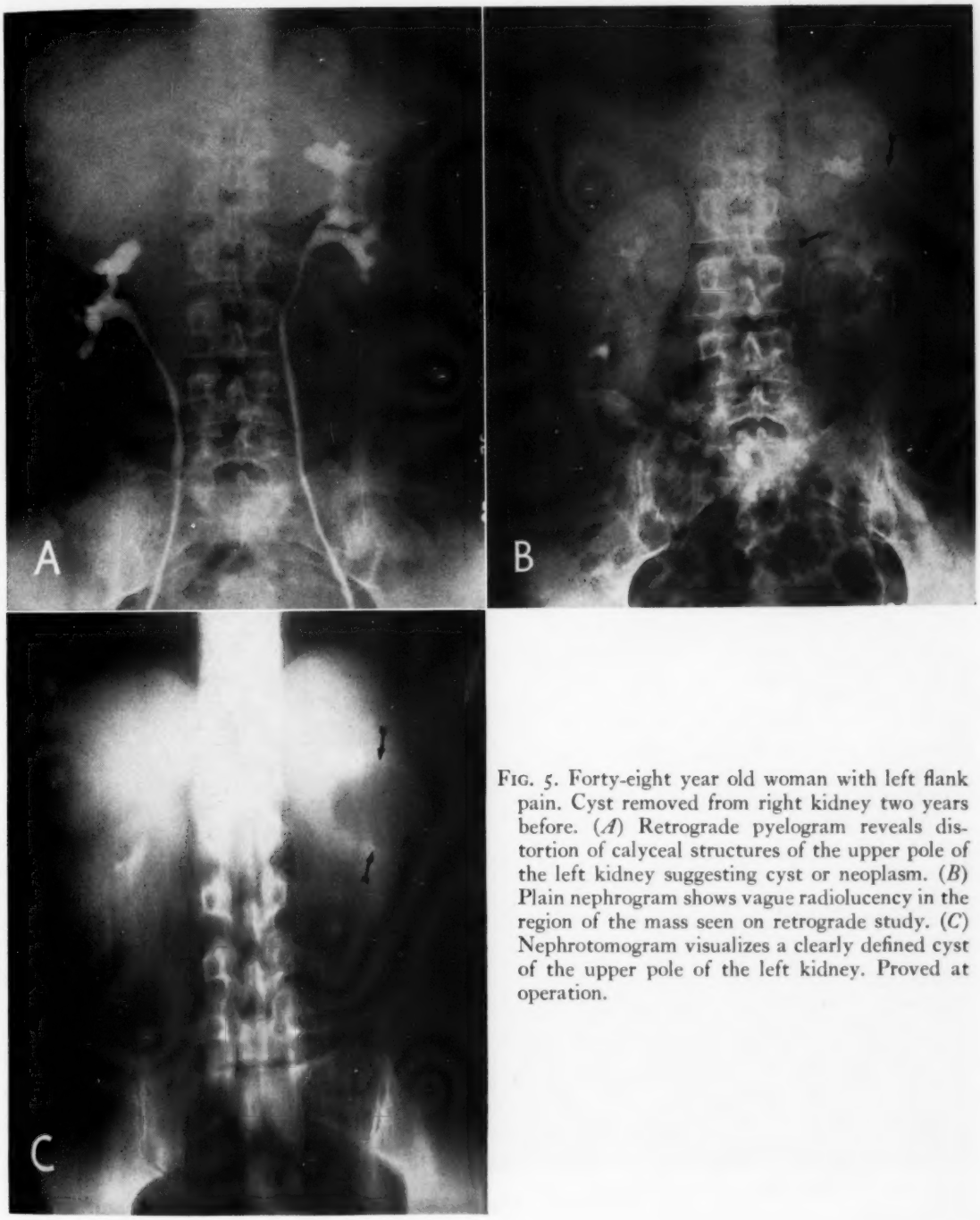

Fig. 5. Forty-eight year old woman with left flank pain. Cyst removed from right kidney two years before. (*A*) Retrograde pyelogram reveals distortion of calyceal structures of the upper pole of the left kidney suggesting cyst or neoplasm. (*B*) Plain nephrogram shows vague radiolucency in the region of the mass seen on retrograde study. (*C*) Nephrotomogram visualizes a clearly defined cyst of the upper pole of the left kidney. Proved at operation.

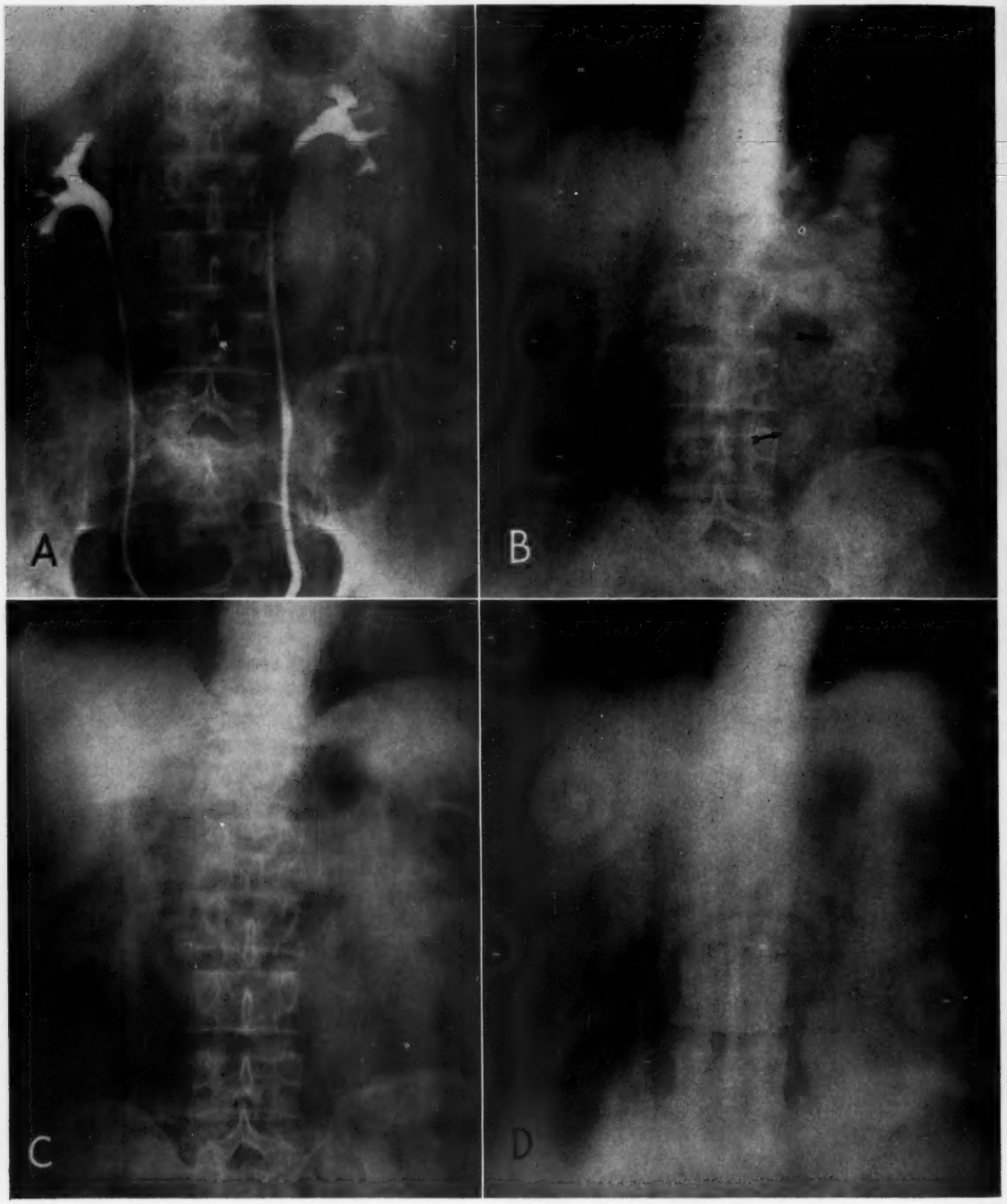

FIG. 6. (*See page 223 for legend*)

Fig. 6. Fifty-eight year old male with left flank mass. (*A*) Retrograde study shows a large mass occupying the lower pole of the left kidney with displacement of calyces cephalad. (*B*) Arteriogram reveals a large collection of abnormal vessels in the mass with puddling of contrast medium in dilated vessels. (*C*) Nephrogram reveals slight opacification of the mass. (*D*) Nephrotomogram more clearly defines the mass which, unlike cysts, has opacified. (*E*) Surgical specimen demonstrating a large carcinoma of the kidney. The vessels have been injected and verify the pathological vascular pattern shown in the arteriogram (*B*).

serial film technique in the arteriogram and nephrogram phase of the procedure. We expect this to produce films at the time of maximum opacification. In addition, it may be of value to use spot roentgenograms of the kidney during the procedure in order to obtain better detail. Future studies will be combined with retropneumoperitoneum in selected cases.

SUMMARY

A technique providing precise delineation of functioning renal parenchyma has been described. Preliminary results of this method in differential diagnoses of renal cysts and neoplasms have been discussed. The results of our present studies have been sufficiently encouraging to warrant extended application of the technique. A more detailed account and critical evaluation of the method will be possible in a subsequent report.

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VENOGRAPHY

A NEW TECHNIQUE*

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VENOGRAPHY and arteriography are being utilized more and more frequently as diagnostic procedures for peripheral vascular disorders. In spite of technical refinements, however, most patients for venographic studies are selected for vein ligation or stripping on the basis of history and physical tests alone. Usefulness of venography has long been demonstrated, and many believe that this procedure should be more frequently used to determine patency of deep veins.

The first reported angiograms were evidently made in January, 1896, when Haschek and Lindenthal[13,14] injected Teichmann's mixture (lime, cinnabar and petroleum) into an amputated hand. Roentgenograms clearly visualized the vessels. Much has appeared in the literature since then. Many reports have been concerned with modifications of technique. These modifications have been use of single exposure with single film,[4,8,16,18,19,22,24,25] simultaneous exposure of several films to outline a complete extremity,[17] single exposure of rapidly changing films,[1,3,9,23] and stereoscopic exposure of two films.[2,5,20]

Our report will describe a new technique which we have found useful and will not review the clinical aspects of this subject.

TECHNIQUE

The new technique involves three factors: an opaque plastic filter, a long film measuring 36 by 14 inches and balanced film exposure.

Use of the opaque plastic filter (Fig. 1), was suggested by one of us (R.J.R.). This filter has been used in roentgenography of the entire body,[10] the spine,[6,11] arterial circulation,[12] the chest,[15] and placenta visualization.[6,7] Reeves and Cahoon[21] describe a filter consisting of an aluminum diaphragm, 0.5 mm. thick, upon which is drawn a circle, the size of the tube end of the cone. The circle is bisected. An opaque plastic is

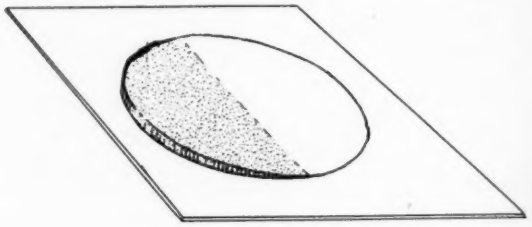

FIG. 1. Opaque plastic filter.

spread on one-half of the circle and is molded so that the outer edge is about 2 mm. thick and tapered gradually to a thin edge at the inner straight side of the half circle. This filter is placed in the filter slot of the tube with the plastic in the direction of the lower leg.

The long film (36 by 14 in.) and a long Bucky were employed to record the entire venous supply of a limb on one film. Use of this film was practical when the plastic filter was employed to selectively obstruct the roentgen rays to the leg more than to the upper thigh and pelvis.

Manual changing of cassettes is slow and film expensive. Therefore, consideration was given to the principle of time exposure as used in ordinary photography to record the path of moving objects. Movement of radiopaque material along the

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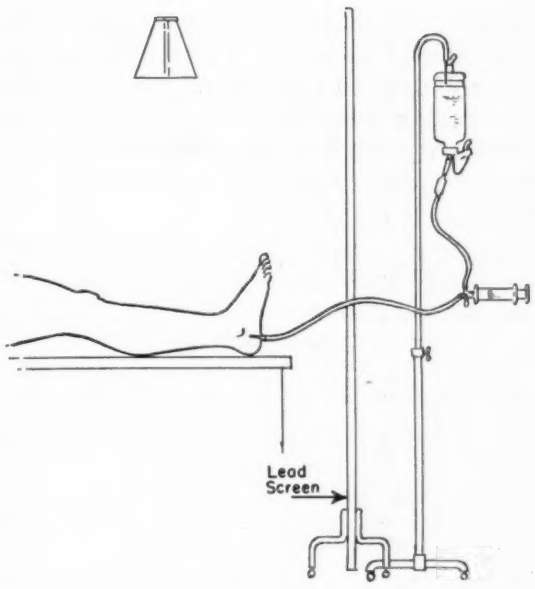

Fig. 2.

course of a vein is relatively slow, and prolonged roentgenographic exposure is impractical. The principle of multiple exposure rather than time exposure was suggested by one of us (R.L.P.)

METHOD

Using local anesthesia a small incision is made behind the lateral malleolus exposing the origin of the small saphenous vein. The vessel is dissected free and its distal end is ligated. The proximal portion is incised and a No. 16 polyethylene tubing is introduced. A stopcock is attached to one end of the tubing and this in turn is connected to a bottle of dextrose solution (Fig. 2). A continuous drip is begun to keep the tube patent. The tube is secured by a ligature around the proximal portion of the vein.

The injection material used is 40 cc. of 50 per cent diodrast compound.* It is given with continuous firm pressure, usually within forty-five seconds. After the first 20 cc. has been administered a first exposure is made. Another exposure is made at completion of the injection. The third exposure is made thirty seconds after completion of the injection. This requires a triple exposure of the film. The cassette is then changed, manually, usually within thirty seconds. The second film is then exposed three times at thirty second intervals. If marked delay of venous flow is suspected, a third film is then triple exposed in a similar manner. Reproductive organs are covered with a lead sheet.

By trial and error it has been determined that satisfactory venograms can be

Fig. 3. Venogram revealing no obstruction of the deep veins.

* This was supplied by Winthrop-Stearns, Inc.

FIG. 4. Venogram showing obstruction of femoral vein, left leg, at mid-thigh level.

obtained with a kilovoltage of 70 and a time of one-half second. With these constant the milliamperage is varied between 150 and 300. The target-film distance is maintained at 5 feet.

Figures 3 and 4 demonstrate the satisfactory penetration of thigh and calf using the barium plastic filter and the triple exposure.

SUMMARY

A technique for venography is described. The method utilizes a large cassette (36 by 14 in.), a barium plastic filter and triple exposure of each film. The barium plastic filter is used to compensate for the densities of the thigh and calf. The triple exposure is used to accomplish visualization of the entire deep venous system of the leg on a single film.

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ARTIFICIAL NEPHROGRAPHY BY COMBINED RETROGRADE AND INTRAVENOUS UROGRAPHY*

PRELIMINARY REPORT

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THE roentgen visualization of the kidney tissue by means of an artificial nephrogram is still in an unsatisfactory experimental stage. The lack of a simple technique, and the need of finding one, has been recognized by many authors. The aim is to obtain sufficient contrast medium saturation of the kidney tissue. As is known by present routine methods, such as intravenous and retrograde pyelography, tumors in the kidney parenchyma must be of sufficient size to distort the kidney pelvis or calyces to be diagnosed. By means of nephrography, the small parenchymal tumors may be detected. In 1942, Hellmer[3] observed on excretory urograms of patients with acute ureteral obstruction that there was retention of the opaque medium in the renal parenchyma of the involved side, a spontaneous nephrogram. He detected a cyst and a tumor as defects in opacification of the kidney tissue. The imitation of this condition by means of artificial ureteral obstruction was investigated by a group of authors (Hickel[4,5]), Weens and Florence,[10] and Leighton.[6] Another group of authors (Dos Santos,[1] Sante,[7] Smith *et al.*[8,9]) produced excellent artificial nephrograms by means of translumbar arteriography. More recently Wall and Rose[11] described a valuable technique employing rapid intravenous injection of 70 per cent urokon sodium.

Any of the methods previously described by the above authors were original and fully suited for the desired purpose, the production of an artificial nephrogram.

The method here described for producing an artificial nephrogram is basically similar to that proposed by the first group of authors.[4,5,6,10]

TECHNIQUE

After completion of the routine unilateral retrograde pyelogram, using the largest ureteral catheter possible, the catheter is left in place. The tip of the ureteral catheter should reach the ureteropelvic junction in order to obtain a sufficient back pressure in the kidney pelvis. The next step is to clamp the free end of the ureteral catheter in order to prevent escape of the contrast medium from the kidney pelvis and calyces. This can also be done by leaving the syringe and needle in the free end of the ureteral catheter and attaching the plunger to the barrel of the syringe by means of adhesive tape. The ureter is practically obstructed and a sufficient back pressure in the kidney pelvis is obtained with this technique.

At this time, the routine films are taken. Thirty cubic centimeters of diodrast or other routinely used contrast medium is administered intravenously. Films are then taken in fifteen, twenty-five and thirty-five minute intervals, until optimal saturation of the kidney tissue has been obtained. It should be noted that a nephrogram of one kidney should be obtained at a time, thus leaving the other kidney functioning. In Figure 1, films are shown which illustrate the difference in contrast density of the routine intravenous and retrograde pyelograms in a normal kidney, as compared with each other and with an artificial nephrogram by this technique.

CASE REPORT

The following case demonstrates the applicability of the combined retrograde and intravenous urogram.

A.C., a male, aged fifty-two, barber, was admitted to the hospital on January 8, 1952,

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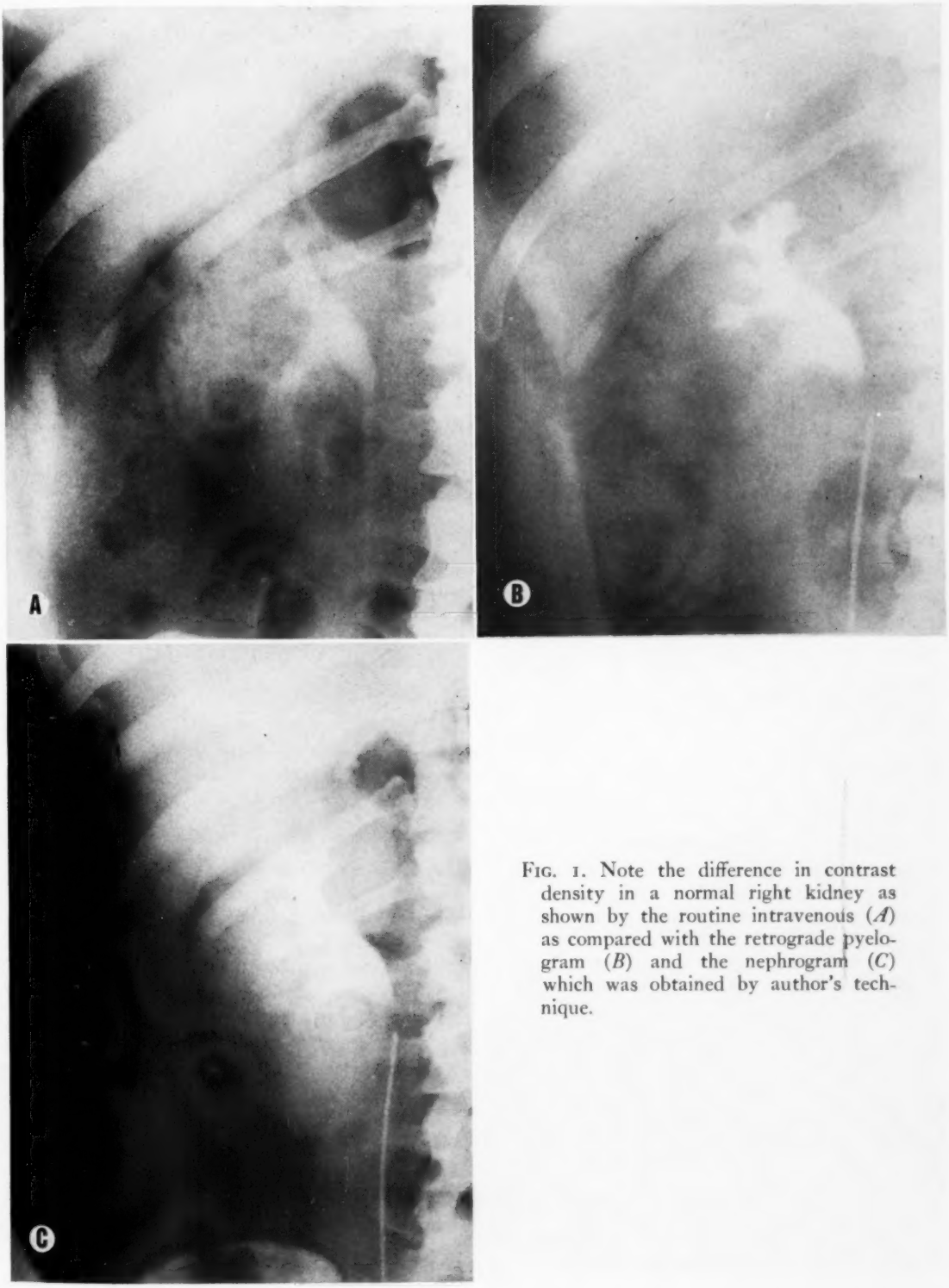

Fig. 1. Note the difference in contrast density in a normal right kidney as shown by the routine intravenous (*A*) as compared with the retrograde pyelogram (*B*) and the nephrogram (*C*) which was obtained by author's technique.

FIG. 2. Case A. C. Flat film of the gallbladder region illustrating a round, lobulated soft tissue mass.

complaining of "gas pains" of two months' duration. The pain started in the right hypogastric region and then radiated into the chest. There was no history of hematuria, frequency, dysuria or trouble starting and stopping the stream. He stated that there was a small purulent discharge immediately following urination.

The past history revealed that in 1941, when the patient was operated on for an acute appendicitis, an undescended right testicle was discovered and removed. There was no history of any other congenital anomaly. In the same year a small benign tumor was removed from the patient's right breast.

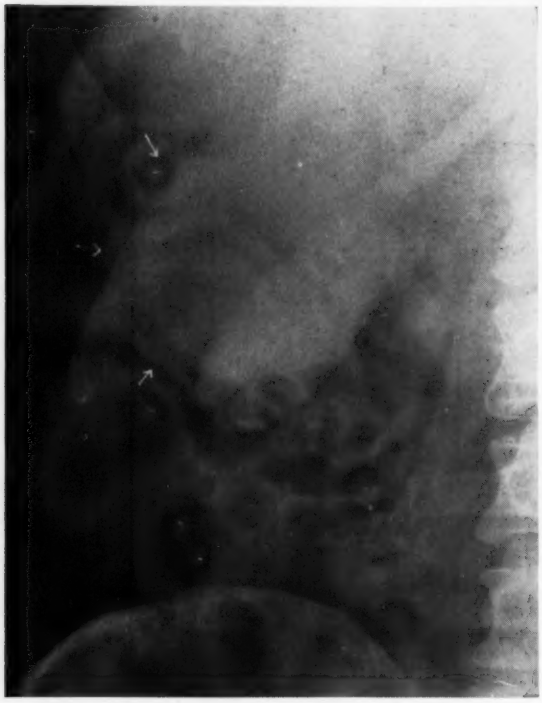

FIG. 3. Case A. C. Cholecystogram. The soft tissue mass is again visible, not being in connection with the gallbladder.

FIG. 4. Case A. C. Intravenous urogram. The mass appears to be connected with the renal shadow, without distortion of the calyces and pelvis.

Physical Examination. Temperature was normal. He was well developed, without any signs of recent loss of weight. Skin color healthy. No changes in the heart or lungs. The abdomen was normal. No palpable mass felt. Blood pressure 140/80. Head, eyes, ears negative.

Laboratory Findings. Urinalysis: color clear and yellow, reaction 6.2, specific gravity 1.014, albumin, sugar, and acetone negative, leukocytes 1 to 2 per high power field, erythrocytes 1 to 2 per high power field. Hemogram: hemoglobin 85 per cent, erythrocytes 5.37 million,

Fig. 5. Case A. C. Retrograde pyelogram. No remarkable changes from the intravenous urogram as shown in Figure 4.

leukocytes 4,900, neutrophils 68 per cent, lymphocytes and monocytes 4 per cent.

Roentgen Findings. The patient was referred to the Department of Roentgenology for examination of the gallbladder. On the flat film of the gallbladder region, a round lobulated soft tissue mass measuring 6 by 6 cm. was identified (Fig. 2). Whether this mass originated from the gallbladder, liver or kidney could not be determined. The following cholecystogram excluded gallbladder pathology (Fig. 3). Intravenous urography was performed which showed again the previously mentioned soft tissue mass, without distortion of the calyces and pelvis. The mass appeared to be connected with the renal shadow (Fig. 4).

Next, a retrograde pyelogram was obtained which showed only a suggestion of minimal distortion of a lower calyx (Fig. 5). Immediately following the retrograde pyelogram, 30 cc. of diodrast was given intravenously and then films were taken in twenty-five and thirty-five minutes as previously described. On these films, sufficient opacification of the kidney parenchyma was visualized, with a round filling defect demonstrating the presence of a nonfunctioning mass within the kidney parenchyma. The appearance was that of a renal tumor, more likely a renal cyst than a true neoplasm (Fig. 6). At operation a renal cyst was found.

In reviewing the gallbladder films taken in 1949, it was noted that the soft tissue mass had been present at that time. In comparison with the more recent films, no increase in the size of the mass could be determined.

DISCUSSION

The advantages of the above described combined retrograde and intravenous urograms are:

1. The new method emphasizes the simultaneous use of two contrast media of different iodine concentrations such as skiodan and diodrast, thus producing a more marked contrast difference between the kidney parenchyma and pelvis.

2. No side effects have been noted and

Fig. 6. Case A. C. Nephrogram by combined retrograde and intravenous urography, demonstrating a round filling defect within the kidney parenchyma.

FIG. 7. Case A. C. Nephrogram obtained by means of repeatedly administered diodrast, discussed in the text.

there is no pain associated with the examination.

3. The contrast medium saturation of the kidney tissue remains constant until the retrograde contrast medium is released at the discretion of the radiologist. Thus, as many films can be obtained during the one sitting as are desired, including laminagrams.

4. The patient is not hindered in his movements in obtaining different views.

5. The obtained nephrogram and pyelogram makes it possible to demonstrate the excretory portion of the kidney. The opacified kidney shadow may be easily differentiated from extrarenal masses and from the adrenals.

Although the author feels that the most satisfactory nephrograms are obtained by the consecutive retrograde and intravenous urogram method, a sufficient contrast medium saturation of the kidney tissue may also be obtained without the retrograde administration of the contrast medium. Here the largest ureteral catheter possible is placed with the tip at the ureteral pelvic junction and the free end is clamped. Then 30 or 40 cc. of diodrast is given intravenously and films are taken at fifteen, twenty-five and thirty-five minute intervals.

An attempt was also made to obtain an artificial nephrogram following the removal of the ureteral catheter by retaining the contrast medium in the kidney pelvis with external abdominal compression. The compression of the lower ureters may be obtained by means of a manometer cuff applied beneath a pressure band. This procedure is still under investigation.

A third method is to repeat the intravenous administration of the contrast medium. Again, a constant pressure is applied to the lower ureters as described above. Then in once or twice repeated doses, 30 cc. of the contrast medium is given at twenty-five or thirty-five minute intervals (Fig. 7).

The important factors influencing the density of the nephrograms are:

1. *The contrast medium used.* In the cases reported in this paper 35 per cent diodrast was used. Studies with higher concentrated (70–75 per cent) media, are now being conducted. A more opaque nontoxic contrast medium is desired. Reviewing all the available spontaneous nephrograms and comparing them to those obtained artificially, there was no great difference observed in contrast density.

The repeated injection of diodrast increased considerably the density of the nephrogram in a case of delayed excretion due to ureteral obstruction (Fig. 8).

2. *Optimal time of the examination.* This is approximately 25 to 35 minutes following the intravenous administration of the contrast medium. A more adequate contrast medium combination might eventually reduce this time.

3. *Grade of the ureteral obstruction.* A sufficient degree of ureteral obstruction to prevent escape of the contrast medium from the kidney pelvis must be present.

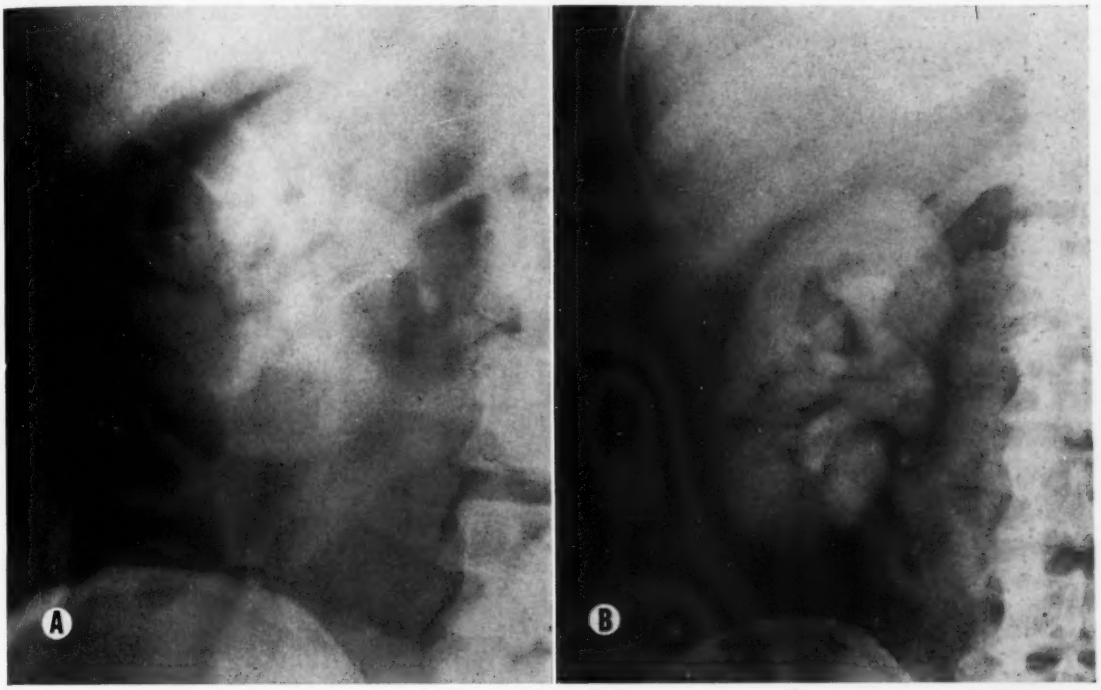

Fig. 8. Two different spontaneous nephrograms: (*A*) obtained forty-five minutes after a single injection of diodrast; (*B*) obtained forty-five minutes after a second injection of diodrast. The second injection was given thirty-five minutes after the first. Note the considerably increased opacification of the kidney tissue.

This is obtained by using the largest possible ureteral catheter. Hickel found that in order to obtain a nephrogram the hydrostatic pressure in the kidney pelvis must reach 60 mm. Hg.

4. *The excretory ability of the kidney parenchyma.* If the kidney tissue is damaged, the excretion of the contrast medium is delayed or blocked completely, depending on the severity of the kidney damage.

I would like to emphasize again the importance of obstructing only one ureter, thus leaving the other kidney functioning. The possibility of precipitation of the contrast medium in the kidney tubules during a simultaneous bilateral nephrography should be kept in mind. Using the nonprotein nitrogen determination as an index of kidney function, there has been no evident change following the unilateral artificial nephrography.

SUMMARY

1. A new method is described for producing an artificial nephrogram.

2. The advantages of this method are briefly discussed.

3. The applicability of this technique is demonstrated in normal and pathological conditions.

4. Other approaches for obtaining artificial retention of the contrast medium in the kidney tissue are briefly discussed.

5. It is felt, however, that further investigations applied to a larger number of cases might prove this technique valuable as a diagnostic aid.

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THE USE OF HYDROGEN PEROXIDE FOR THE ELIMINATION OF GAS FROM THE INTESTINE DURING ROENTGENOGRAPHY OF THE ABDOMINAL VISCERA

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GAS in the intestine is a source of annoyance in roentgenography of the abdominal viscera because often it obscures important outlines and details of pathological changes on which dependence is made for diagnosis.

Several suggestions have been put forward to explain its presence, the more important features stressed have been:

(1) The swallowing of air.
(2) Intestinal respiration.
(3) Fermentation of intestinal contents.

FIG. 1. Roentgenogram taken at the completion of urography thirty minutes after intravenous injection, showing the absence of gas in the intestine.

FIG. 2. Showing a considerable amount of gas in the small intestine, fifteen minutes after the patient had been asked to swallow air.

(1) *The swallowing of air* is frequently observed during roentgenoscopy. It is an important factor. Passage of the air through the alimentary tract can be studied by serial roentgenography of any volunteer as is shown in Figures 2 to 4. Wangensteen and Lea[5] and Magnusson[3] have stressed its importance and shown how necessary it is to instruct the patient to avoid swallowing before and during the course of roentgenography of abdominal viscera.

(2) *Intestinal Respiration.* This is the

FIG. 3. Thirty minutes after aerophagy.

term applied by Begg[1] to the interchange of gas which takes place between the blood and the interior of the intestine. Evidence of this has been provided by the studies of McIver, Redfield and Benedict,[2] and Pogrund and Steggerda.[4] These authors have found that oxygen and carbon dioxide are very quickly absorbed by the blood stream, whereas the absorption of nitrogen is slower and less complete. It was the work of these authors which prompted one of us (A.G.) to experiment on the use of hydrogen peroxide in the manner to be described.

(3) *Fermentation of Intestinal Contents.* The importance of this has been apparent to all radiologists. The excessive fermentation which is known to occur following the consumption of legumes should be sufficient to exclude these from the diet for the two days preceding the examination.

Assuming that intestinal fermentation was the chief cause of the gas, many devoted their attention to the washing out of the bowel before roentgenography, but in some cases it seemed that this treatment often led to the appearance of more gas than was seen in the unprepared patient. Aperients and some enemas often produce the same effect; indeed, it would seem in some cases that they produced upper abdominal discomfort which incited air swallowing with all its disadvantages.

Low residue diets have been employed to limit possible intestinal fermentation, and charcoal has been administered to absorb such gas as is formed. Some success was claimed from the administration of takadiastase. The variety of the methods employed to get rid of this gas or avoid its production indicates that none of the methods have met with the success desired. More recently tannic acid has been employed. With this it is often possible to get rid of gas and, in the case of the colon investigations with barium enemas, to obtain good pattern outlines of the mucosa, but the use of this agent is sometimes associated with the pains of colic.

The agent employed must be simple to use, harmless, easily obtained and of little cost; it should exercise no effects on the other abdominal viscera but be effective in

FIG. 4. Air is now present in considerable quantity in the large intestine.

cleansing the colon of gas. In searching for the agent with these properties which would act directly upon the colon causing the absorption of gas into the blood stream and assist with its elimination, one of us (A.G.) focussed his attention and investigations on hydrogen peroxide and secured results which appeared to be more successful than any other. The method which he found to give the best results was as follows:

The patient was given an enema at body temperature, the fluid used consisting of 10 cc. of H_2O_2 (40 vol.) per liter of water. This is introduced very slowly, the patient being encouraged to change position from prone, left side, supine and right side. When the whole of the enema has been introduced the patient lies for a short time on the right side. It is important, however, that the patient should evacuate the enema on the first symptoms of vague abdominal colic because it was found that if this precaution was neglected the colic is readily followed by a diffuse atony of the colon with a resulting defective elimination of the gases. The pH of the solution is about 7 (measured with the bromthymol method).

Fig. 6. Demonstrating the almost complete colonic gas clearance following the injection and evacuation of 2½ pints of hydrogen peroxide solution (25 minims of H_2O_2 to the pint).

Fig. 5. Preliminary roentgenogram prior to pyelography.

In the 300 cases reported (by A.G.) to the Grappo Radiologi Emiliani-Marchigiani, Florence, February, 1952, no complication was observed. In those cases with atony of the bowel in whom the first enema did not produce the desired effect, a second enema could be given and success so achieved. Insufficient evacuation of the colonic contents is apt to be associated with gas in the colon.

At the Queen Elizabeth Hospital we secured success (Fig. 5 and 6) with the lesser concentration of 25 minims of H_2O_2 (20 vol.) to each pint of water, but when an accumulation of feces was noted on the preliminary film a preceding colonic washing was given.

The hydrogen peroxide may act by producing a neuromuscular excitation of the

FIG. 7. Colon outlined by barium sulfate solution containing hydrogen peroxide in a similar concentration as stated in Figure 6.

FIG. 8. Roentgenogram taken after evacuation, showing the mucosal pattern of the large intestine.

colon which stimulates evacuation of its contents and perhaps to a minor extent, by increasing the tension of the colon, lead to a quicker transfer of the gas from the colon to the blood.

To ensure success with this method attention should be given to the diet for the two days preceding the examination, excluding such things as legumes in order to ensure a low residue in the colon. Further, the disturbing effects of air swallowing should be explained to the patient and his attention sought in avoiding it. We recommend the technique as a preliminary preparation for the patient undergoing roentgenological investigation of the urinary tract.

Hydrogen peroxide can usefully be employed in the concentration suggested in the barium enema used for visualization of the colon. With it, effective evacuation of the bowel and a very good mucosal pattern of the whole colon is secured in which relatively small localized irregularities can be detected (Fig. 7 and 8). It has all the advantages which have been claimed for tannic acid with none of its disadvantages.

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CARBONATED SOFT DRINKS IN ROENTGEN DIAGNOSIS OF FOREIGN BODIES IN THE STOMACH

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SINCE the original report[1] of the use of carbonated soft drinks as a contrast medium in the roentgen localization of radiopaque foreign bodies in the abdominal visceral cavity, I have found other interesting uses. In addition, experience has emphasized very emphatically the proper amount of the carbonated soft drink to be used.

Originally, my greatest problem was to find a contrast medium for proving a foreign body either in the stomach or not. Such a medium should not obliterate the foreign body shadow, should not interfere with subsequent endoscopy for removal by obscuring the foreign body for the roentgenoscopist, or endanger the patient if an anesthetic needs to be given.

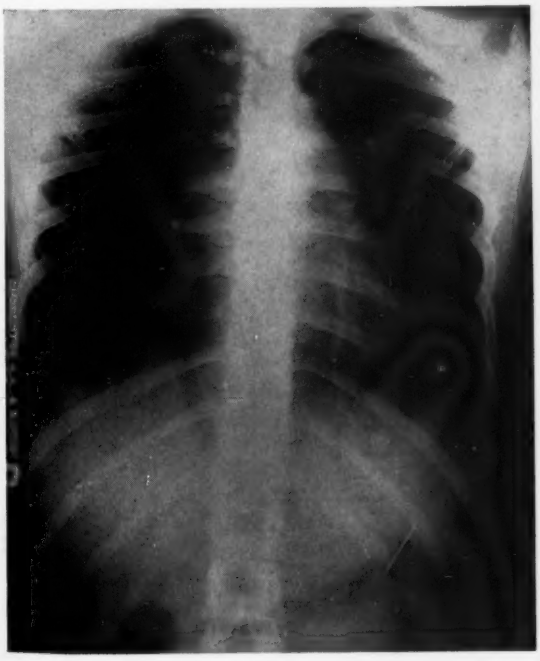

FIG. 1. Case 1. Straight pin upper left quadrant of the abdominal cavity.

Many times in this clinic in the years prior to the use of carbonated soft drinks as a contrast medium, much valuable time was lost in attempting to remove magnetic foreign bodies thought to be in the stomach but which were actually beyond the stomach. In addition, there was the discomfort to the patient of an unnecessary procedure if, after introduction of the Alnico magnet, the foreign body was proved to be beyond the stomach. Now with the use of carbonated soft drinks as a contrast medium, we know before the attempted removal whether or not the foreign body is in the stomach. Most of the time films without a contrast medium are worthless (Fig. 1).

FIG. 2. Case 1. Stomach outlined with gas liberated from a carbonated soft drink. The pin is not in the stomach.

Fig. 3. Case I. After purposely giving too much of the carbonated soft drink. This film suggests that the pin is within the stomach according to the gas shadow. Compare with Figure 2.

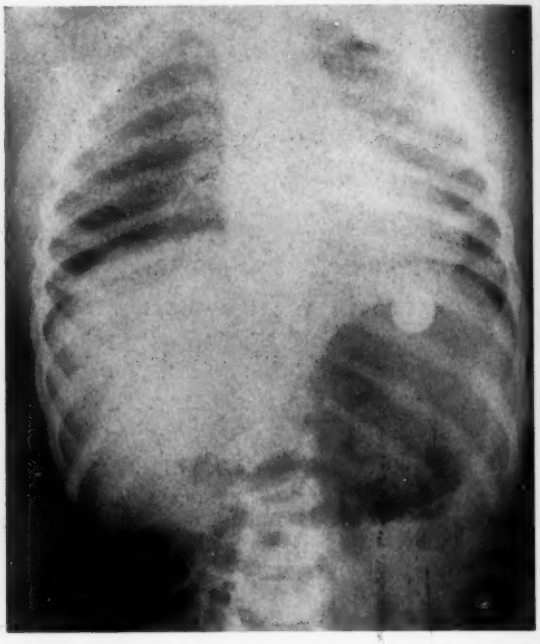

Fig. 5. Case II. Same patient as Figure 4 after giving a carbonated soft drink. By contrast the foreign body is plainly visible (marble).

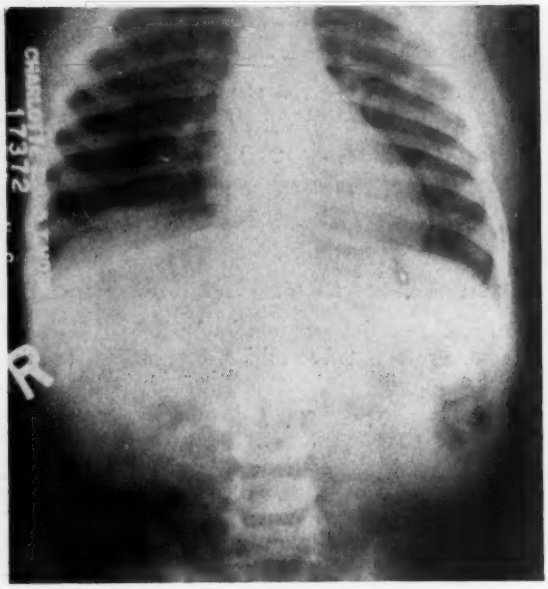

Fig. 4. Case II. Film of a suspected foreign body in the stomach. No foreign body demonstrable (marble).

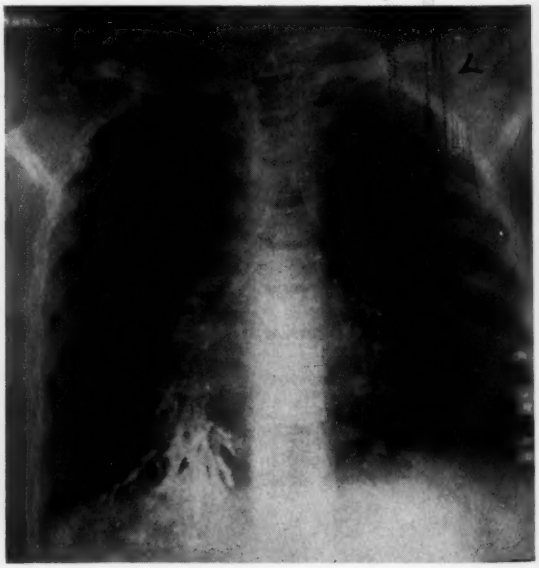

Fig. 6. Case III. Bronchogram; heart on the right side.

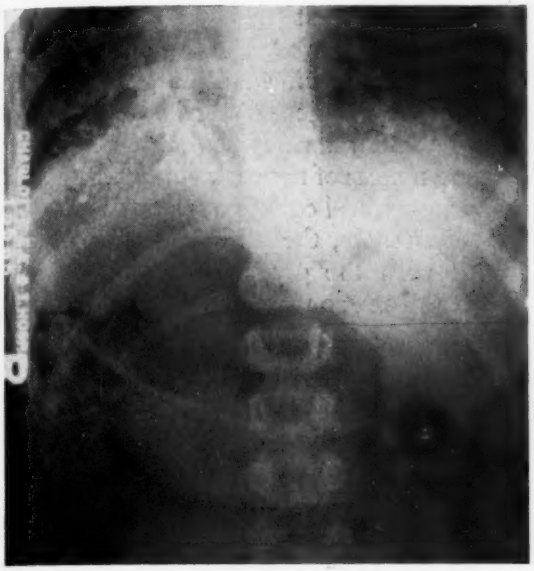

Fig. 7. Case III. Same case as Figure 6. Stomach outlined with gas (carbonated soft drink). Situs inversus viscerum.

The straight pin seen in Figure 1 was at first thought to be in the stomach. To be absolutely sure, the patient, a sixteen year old girl, was given 1 ounce of a very cold carbonated soft drink. After the lapse of thirty seconds, films were taken (Fig. 2). These films revealed the pin beyond the stomach in the intestine. I cannot stress several points too vigorously at this time. First, the carbonated soft drink should be very cold. This permits the body heat to liberate the gas a little more slowly, and by so doing, eliminates eructation of the liberated gas. Second, not too much of the carbonated soft drink should be given. This is most important. The amount of distention from a small amount of a carbonated soft drink is unbelievable until some experience is gained in the use of this contrast medium. Children under a year old need only two or three swallows, and even in adults, it is rare that more than an ounce is given.

To emphasize this point, the same patient as shown in Figures 1 and 2 was permitted, after the pin was localized, to drink about 3 ounces of the carbonated soft drink. This film (Fig. 3), taken immediately after Figure 2 and the ingestion of more of the carbonated drink, suggested that the pin was in the stomach. This emphasizes very vividly that too much should not be given as it causes extreme distention of the stomach, thereby producing an overlapping of the shadows. In addition to leading to a wrong diagnosis, the large amount may interfere with subsequent endoscopy because of possible aspiration complications.

Another interesting use that I have found for carbonated soft drinks is in cases of foreign bodies in the stomach which are only slightly radiopaque or radiopaque by contrast only.

Figure 4 is a roentgenogram of a two year old child who complained of swallowing a marble. No evidence could be found of any radiopaque foreign body in the abdominal visceral cavity on this film. After considerable questioning of the mother, she still insisted that the child had swallowed a marble. In an attempt to satisfy the mother, the referring physician and ourselves, I decided to see if we could demonstrate a foreign body of slight radiopacity by contrast. Consequently, we gave the

Fig. 8. Case IV. Radiopaque foreign body in the upper left quadrant of the abdominal visceral cavity. Foreign body swallowed immediately following an unusually heavy meal.

Fig. 9. Case IV. Film made after the patient drank 2 ounces of a carbonated soft drink. The large amount of food mixed with the gas, keeping the gas from revealing the stomach outline.

patient a small amount of a cold carbonated soft drink, approximately 1 ounce. Much to my surprise, this film revealed a marble in the fundus of the stomach (Fig. 5).

The case shown in Figures 6 and 7, of situs inversus viscerum, is included merely to illustrate the ease with which a stomach may be outlined with a carbonated soft drink and also as an interesting finding along with the bronchogram. This patient, a young child, refused barium but willingly cooperated when offered a soft drink.

The only case in which the carbonated soft drink failed to reveal the stomach outline during our five years of experience with this contrast medium was an adult who had swallowed a foreign body very shortly after an unusually large meal. The foreign body, a piece of steel wire, is shown in the original film (Fig. 8). After drinking about 2 ounces of the carbonated soft drink, the stomach still could not be outlined (Fig. 9). Apparently, the unusually heavy meal mixed with the gas, thus failing to give further distention of the stomach or demonstration of the stomach outline.

CONCLUSION

One of the most important facts to be remembered in the use of carbonated soft drinks, as a contrast medium, for localizing foreign bodies in the abdominal visceral cavity is to use them in small quantities. Large amounts frequently give false impressions.

Another important factor is to give the carbonated drink cold.

This medium is valuable in demonstrating, by contrast, foreign bodies of slight radiopacity.

This contrast medium is a convenient one for demonstrating the stomach outline where position is the only consideration, as in situs inversus viscerum.

Carbonated soft drinks may be of little value immediately after a heavy meal.

106 West 7th St.
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REFERENCE

1. Roberts, W. E. Carbonated soft drinks as contrast medium for localization of magnetic foreign bodies in abdominal visceral cavity. *Laryngoscope*, 1948, *58*, 155–161.

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TREATMENT OF CARCINOMA OF THE TONGUE*

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THIS paper is based on the study of 113 cases of carcinoma of the tongue treated at the Radium Institute between May, 1930, and December, 1944.

INCIDENCE

Statistics of our Institute show that carcinoma of the tongue is not a frequent disease. Among 10,000 cancer patients who consulted us in a fourteen year period (1930–1944) only 1 per cent of the whole group was diagnosed as lingual cancer.

SEX AND AGE

Among 113 cases there are 15 women (13.2 per cent) and as to frequency in different periods of life, we have found that the larger group of cases belongs to the decade between fifty and fifty-nine years of age (Table 1).

TABLE I

Age	Number of Patients
10–19	1
20–29	1
30–39	3
40–49	17
50–59	51
60–69	29
70–79	8
80–89	2
Not stated	1
Total	113

LOCALIZATION

The disease starts most frequently in the lateral borders and preferably in its middle third.

CAUSATIVE FACTORS

In our opinion the most important local factors are leukoplakia and mechanical irritation against a sharp tooth.

Leukoplakia appears in 12 of our cases but we think that this diagnosis has been omitted in several other cases mostly because the tumor itself has destroyed the pre-existing leukoplakia.

The second predisposing factor is the mechanical trauma against a sharp tooth. Of these we have 18 cases to which we can add 4 more in which cancer appeared at the site of a recent bite.

For a long time syphilis has also been thought to be a predisposing factor. Thirty per cent of our cases had positive serologic reactions but we see no basis for believing that syphilis is a real causative factor. Among the medical profession this erroneous conception of syphilis as a causative factor has done much harm because biopsy is delayed while antiluetic treatment is being given.

PATHOLOGY

Biopsy was not performed in 11 cases of our series. These were terminal cases in which no treatment was given. Among the remaining cases most of the histopathologic types were differentiated squamous carcinomas, Grade 1 or 2 of Broders (Table II).

TABLE II

PATHOLOGICAL REPORTS

	Cases
Epidermoid grade 1 or 2	85
Epidermoid grade 3 or 4	13
Reticulum sarcoma	1
Lymphoma	1
Not stated	13
Total	113

* Presented at the Third Inter-American Congress of Radiology, Santiago, Chile, November, 1949.

SYMPTOMS

Lingual cancer appears as an ulcerated lesion without any specific features. We feel that any ulceration in the tongue that has no tendency to spontaneous healing ought to be considered as suspicious of cancer and the area should be biopsied.

Cervical lymph node metastasis is sometimes the first symptom that attracts the patient's attention. This is just a complication in the evolution of the disease. In case of doubt as to the nature of a cervical mass, oral cavity and nasopharynx should be checked carefully. Aspiration biopsy of the cervical mass is the best procedure for an accurate diagnosis.

DIAGNOSIS

In our series the average patient waits 6.3 months before consulting a physician. The earliest case sought medical advice fifteen days after symptoms appeared. On the other hand, we have a case in which four years elapsed before medical care was sought. There is another delay for which the medical profession is responsible. Many times the first physician consulted makes an erroneous diagnosis—syphilis in most cases—and does not refer the patient to a cancer institution until antiluetic treatment has been given without any benefit.

TREATMENT

Three procedures have been employed in treating the primary lingual carcinoma: insertion of radium needles, roentgen therapy and surgery.

We feel that surgery is indicated in small lesions less than 2 centimeters in diameter, mainly located in the tip or anterior third of the tongue. It is also a definite indication in cases where radiation therapy has already failed. In such instances, surgical excision, no matter how extensive, is preferable to a second course of irradiation, provided, of course, that the disease is still in a local stage. There is a third indication for surgery—cases in which local disease has invaded the mucosa of the gum or the bony structure of the mandible. We believe that radiation therapy has little to offer in such patients. A few of these can be definitely cured by means of radical surgery: removal of the primary lesion together with the mandible and the affected lymph nodes.

In our experience, insertion of radium needles has proved to be the most effective radiation treatment for the primary lesion. Among 66 cases treated with radium needles we obtained 79 per cent local recovery, while among 29 patients treated with external roentgen therapy we only had 57 per cent recovery. However, it must be remembered that this comparison is not referred to similar cases because a number of the patients treated with roentgen rays were more advanced than those chosen for radium needles. Besides, this figure of 79 per cent local recovery has no definite value. Most of our cases, as may be seen in Table VI, died within the first two years of treatment.

Radium needles were inserted in the thickness and about the external limit of the tumor, always parallel to each other and keeping a distance of 1 cm. between them. Total time of treatment is about eight days, and the total dose is 0.8 to 1 millicurie per centimeter of focal length inserted. The dose expressed in millicuries destroyed fluctuates between 6 and 58, this depending mainly on the volume of irradiated tissue.

The strength of our needles is 0.66, to 1.33 and 2.66 mg. of radium element. The focal length is 2 cm. for the 0.66 and 1.33 mg. needles, and 4 cm. for the needles with 2.66 mg. of radium. All our needles have a filtration equivalent to 0.5 mm. of platinum.

Roentgen therapy was given as follows: 200 kv., 10 ma., 50 cm. distance; 0.5 mm. of copper as filter; two lateral fields; daily dose, 300 to 400 r with one treatment per day. Average total dose per field on the skin surface: 2,000 to 6,000 r. Total time of treatment: three to four weeks.

Tabulation of cases is given in Table VI. For better understanding we call attention

to the different vertical columns. The first 6 columns are self explanatory. The column on dates has two figures: the first number represents the month and the second the year. The eighth vertical column shows the dose on interstitial radium treatment expressed in millicuries destroyed. The next column shows the number of roentgens given on the skin surface. In cases in which the number of roentgens was not available, as in Case 1837, the figure represents the date of treatment.

Treatment of Lymph Node Metastasis. It should be remembered that in treating carcinoma of the tongue, the primary lesion as well as the lymph node metastasis ought to be considered from the beginning as part of the same problem. In our cases, among 113 patients, 67 of them, or 59.3 per cent had clinical metastasis on first examination. Among the remaining 46 cases

Table III

LYMPH NODE METASTASIS

Total number of patients	113
With metastasis on admission	67 (59.3%)
Without metastasis on admission	46 (40.7%)
Among 46 cases without metastasis on admission 18 (39%) developed metastasis later on	
Total number with metastasis:	85 (75.2%)

without metastasis on admission, 18, or 39 per cent, developed spread to the regional lymph nodes later on. This means that in our series metastases were present in 85 cases which is equivalent to 75 per cent of all cases considered in this study (Table III). The fact that lymph node metastases are present in a large number of cases and that most of our patients do not return at regular intervals for follow up has led us to perform radical neck dissections in all cases of lingual cancer, provided there is a reasonable basis to think that the primary lesion has already been controlled.

We do not perform a radical neck dissection in carcinoma of the base of the tongue with metastasis. In those cases the primary lesion as well as the lymph node area is included when possible in the same beam of roentgen rays. This neck dissection is performed prophylactically in all cases of lingual cancer as soon as the radiation reaction in the tongue has subsided.

Table IV

RADICAL NECK DISSECTION

Number of cases with palpable lymph nodes (clinical metastasis): 38	
Pathological report	
Positive nodes	Nonmetastatic nodes
29 cases	8 cases
In 1 case pathological report is not stated	

Clinical evidence of lack of metastasis does not prove its absence. Among 5 prophylactic neck dissections, 4 had pathological evidence of metastasis. This is another reason for insisting on the value of performing a neck dissection in all cases even without palpable lymph nodes (Table v).

Among 38 cases in which metastases were palpable a radical neck dissection showed that 8 of these did not have microscopic evidence of carcinoma. This means an error of 18.9 per cent which could have been avoided if we had done aspiration biopsy in all enlarged neck nodes prior to operation (Table IV).

The detail as to treatment of lymph node metastases is also shown in Table VI. The roentgens are expressed in terms of roentgens on the skin surface of the neck. By surgery to lymph nodes we mean in most of our cases a radical neck dissection.

The postoperative treatment after neck

Table V

PROPHYLACTIC NECK DISSECTION
(Without Palpable Nodes)

Number of cases: 5	
Pathological report	
Positive: 4 cases	Negative: 1 case

TABLE VI

TABULATION OF CASES

Case Number	Age	Sex	Duration of Disease (months)	Local Factor	Biopsy	Treatment to Tongue			Treatment to Lymph Nodes			Postoperative Treatment to Neck		Results					Cause of Death	Date of Death
						Date	Radium mc. destroyed	Roentgen rays (roentgens)	Roentgens	Surgery	Biopsy	Radium mc. destroyed	Roentgens	Recurrence in tongue	Recurrence in lymph nodes	5 year cure	Lost	Dead		
17	59	M	2½		Epidermoid gr. 1–2	6/30	30.96			+	+	+						+		12/31
22	48	M	2			6/30	17.28										+	+		
29	73	M	8		Epidermoid gr. 1–2	6/30	25.68			7.30	−	+						+	Progression	3/31
31	56	M	3		Epidermoid gr. 1–2	7/30	16.8							+				+		10/32
37	48	M	7		Epidermoid gr. 1–2	7/30	11.52			+	+	+						+		1/31
48	39	M		Sharp tooth	Epidermoid gr. 1–2	8/30	21.6					+		+				+		7/32
74	56	M	½	Sharp tooth								+						+		10/31
89	54	M			Epidermoid gr. 1–2	9/30	17.08							+				+		5/31
92	30	M	12		Epidermoid gr. 1–2	9/30	15.84		5,610											
112	55	M	10	Leukoplakia		Too advanced for treatment						Palliative 11.30 +					+			
130	56	M	5		Epidermoid gr. 3–4	10/30	14.88											+		2/31
131	64	M	3			Treatment interrupted														
150	56	M	5		Epidermoid gr. 3–4	10/30												+		6/32
182	55	M	3		Epidermoid gr. 1–2	10/30	58.32											+		3/31
235	51	M	6		Epidermoid gr. 3–4	1/31	+			+	+	+						+	Spine metastasis	5/39
486	60	M	6	Sharp tooth	Epidermoid gr. 1–2	8/31	28											+	Progression	2/32
560	48	M	20 days			Not treated at this Institute						545						+	Progression	8/38
570	58	F	31		Epidermoid gr. 3–4	10/30	+			+	+									
628	46	M	7			1/32												+	Pulmonary metastasis	
659	58	M	5		Epidermoid gr. 3–4	Too advanced for treatment								+						
696	42	M	24			3/32		9,130							+			+	Pulmonary metastasis	11/32
724	60	M	5		Epidermoid gr. 1–2			11,200		+	+									
732	55	M	6	Leukoplakia	Epidermoid gr. 1–2	6/32											+			
759	50	F	1		Epidermoid gr. 3–4	Too advanced for treatment														
767	42	F	5		Epidermoid gr. 3–4	6/32		8,060										+		9/34
785	63	M	15		Epidermoid gr. 1–2	5/32		9,550							+			+		6/32
842	77	M	6			5/32	+			+	+							+		11/33
866	67	M	3		Epidermoid gr. 1–2	7/32	+					+						+	Pulmonary edema	8/32
1060	40	M	2		Epidermoid gr. 3–4	8/32	+										4.37 +			
1172	65	M	6			4.33	7.68													
1256	57	M	48		Epidermoid gr. 1–2	Too advanced for treatment														
						Too advanced for treatment														

TABLE VI—(*continued*)

Case Number	Age	Sex	Duration of Disease (months)	Local Factor	Biopsy	Treatment to Tongue			Treatment to Lymph Nodes			Postoperative Treatment to Neck		Results					Cause of Death	Date of Death
						Date	Radium mc. destroyed	Roentgen rays (roentgens)	Roentgens	Surgery	Biopsy	Radium mc. destroyed	Roentgens	Recurrence in tongue	Recurrence in lymph nodes	5 year cure	Lost	Dead		
1283	43	M	2	Sharp tooth	Epidermoid gr. 1–2	12/33	19.68			1.35	+				3.35			+		9/35
1321	57	M	3		Epidermoid gr. 1–2	1/34		9,500										+		5/34
1358	51	M	3		Epidermoid gr. 1–2	Too advanced for treatment														
1386	46	M	3	Sharp tooth	Epidermoid gr. 1–2	4/34	23.92			10.34	+	+		+				+		11/34
1469	24	F	4		Epidermoid gr. 3–4	6/34		8,100									+			
1489	67	M	12		Epidermoid gr. 1–2	7/34		9,500								6.41				9/48?
1500	50	M	6		Epidermoid gr. 1–2			9,800									+			
1530	50	M	3	Leukoplakia	Epidermoid gr. 1–2	8/34	8.64			10.34	+	+		3.35				+		11/37
1544	85	F	6			Too advanced for treatment														
1574	51	M			Epidermoid gr. 1–2	10/34	26.88					+						+		2/35
1580	85	M	2		Epidermoid gr. 1–2	10/34						345.6						+		8/35
1604	75	M	6		Epidermoid gr. 1–2	11/34		12,500										+	Progression	6/35
1625	66	M	9			11/34				+	+		10,000					+		3/35
1675	53	M	3		Epidermoid gr. 1–2	1/35	13.2			+	+	522.8					+			
1680	64	M	3		Epidermoid gr. 1–2	1/35	26.88			3.35 4.36	+ +	464			10.35			+	Bone metastasis	11/36
1794	60	M	12		Epidermoid gr. 1–2	4/35	36		3,200									+	Cachexia	12/35
1837	67	M	8	Sharp tooth	Epidermoid gr. 1–2	9/34	6.35 13.44	9.34 +						+				+	Progression	1/36
1886	43	M	4		Epidermoid gr. 1–2	7/35	25.18			8.35 10.35	+ +	550							Pulmonary metastasis	12/35
1947	67	M	8		Epidermoid gr. 1–2	8/35	6.72									+			Intercurrent disease	19/43
1954	65	M	6	Sharp tooth	Epidermoid gr. 1–2	9/35	23.52			5.36 10.35	+ +	343.2	5,400	1.39 Radionecrosis		6.40				
2060	66	M	1		Epidermoid gr. 1–2	11/35	14.44										+			
2228	50	M	2		Epidermoid gr. 3–4	2/36	18.72			+	–			+			+			
2295	59	M	2	Sharp tooth	Epidermoid gr. 1–2	3/36		5,750										+	Progression	2/36
2392	14	F	36		Reticulum sarcoma	5/36		5,800										+	Progression	7/37
2398	65	M	10	Leukoplakia	Epidermoid gr. 1–2	6/36	21.6										+			
2586	76	M	2½		Epidermoid gr. 3–4	9/36		8,700										+	Cachexia	9/36
2832	60	M	2	Sharp tooth	Epidermoid gr. 1–2	2/37	23.04		5.37 3,900	4.37	+		6,300					+	Lymph node metastasis	10/37
2840	60	M	12		Epidermoid gr. 3–4	2/37		6,800										+	Progression	8/37

TABLE VI—(*continued*)

Case Number	Age	Sex	Duration of Disease (months)	Local Factor	Biopsy	Treatment to Tongue			Treatment to Lymph Nodes			Postoperative Treatment to Neck		Results					Cause of Death	Date of Death
						Date	Radium mc. destroyed	Roentgen rays (roentgens)	Roentgens	Surgery	Biopsy	Radium mc. destroyed	Roentgens	Recurrence in tongue	Recurrence in lymph Nodes	5 year cure	Lost	Dead		
2859	73	M	8	Leukoplakia	Epidermoid gr. 1–2	2/37	28.8										+			
2966	47	M	2		Epidermoid gr. 1–2	1/37	14			4.37	+		4,800					+		6/38
2973	58	M	2	Leukoplakia	Epidermoid gr. 1–2	4/37	19.2										+			
3072	57	M	9		Epidermoid gr. 1–2	5/37	14.16			+	+		4,500			4.47		+	Intercurrent disease	4/47
3113	30	M	3		Lymphoma	4/37		4,000							4.38 2.800		+			
3298	74	M	4	Sharp tooth	Epidermoid gr. 1–2	9/37	16.8											+		9/39
3654	53	M	2		Epidermoid gr. 1–2	2/38	6.48										+			
3708	70	M	4		Epidermoid gr. 1–2			8,700									+			
4007	59	M	6	Leukoplakia	Epidermoid gr. 1–2	6/38	21.84			2.39	+		3,000				+			
4238	52	M	9	Sharp tooth	Epidermoid gr. 1–2	11/39	31.2			+	+						+			
4354	51	M	8	Syphilis	Epidermoid gr. 1–2	3/39	11.76										+			
4609	60	M	12	Leukoplakia	Epidermoid gr. 1–2	6/39	16.32			11.40	+				4.41			+		8/41
4643	53	M	1½	Sharp tooth	Epidermoid gr. 1–2	6/39	19.2			10.39	+		5,700					+		8/40
4747	59	M	9			Treated elsewhere									+			+	Metastasis	
4962	60	F	12		Epidermoid gr. 1–2	11/39	25.92			1.40	+		2,700				+			
4978	54	M	12		Epidermoid gr. 1–2	11/39	5.76	9,950	2,400				9.41				+			
5513	56	F	7		Epidermoid gr. 1–2	6/40	9.84			+	−						+			
5630	57	M	8		Epidermoid gr. 1–2	8/40		9,000						1.41				+	Radionecrosis cancer	
5670	54	M	10		Epidermoid gr. 1–2	8/40	22.32										+			
5685	54	M	4		Epidermoid gr. 1–2	8/40		+		+	+		8,800	12.40				+	Lymph node metastasis	2/41
5931	56	F	12		Epidermoid gr. 1–2	11/40	16.8			1.41			2,700	1.41				+	Progression	
5983	52	M	2		Epidermoid gr. 1–2	12/40	17.28			+	−					4.46				
6183	54	M	6	Sharp tooth	Epidermoid gr. 1–2	Treated elsewhere. Too advanced for treatment								+						
6259	42	F	3		Epidermoid gr. 1–2	3/41	Too advanced for treatment													
6276	50	M	9	Sharp tooth	Epidermoid gr. 1–2	8/41	25.2										+			
6328	63	M	6		Epidermoid gr. 1–2	4/41	12.18			+	+		3,900				+			
6403	44	M	17	Leukoplakia	Epidermoid gr. 1–2	5/41		+		+	+		4,500–6 4,800–10					+	Progression	1/42
6612		M	7		Epidermoid gr. 1–2	8/41	Too advanced for treatment													
6702	72	M	12		Epidermoid gr. 1–2	9/41	+							+				+	Cachexia	7/42

TABLE VI—(*continued*)

Case Number	Age	Sex	Duration of Disease (months)	Local Factor	Biopsy	Treatment to Tongue			Treatment to Lymph Nodes			Postoperative Treatment to Neck		Results					Cause of Death	Date of Death
						Date	Radium mc. destroyed	Roentgen rays (roentgens)	Roentgens	Surgery	Biopsy	Radium mc destroyed	Roentgens	Recurrence in tongue	Recurrence in lymph nodes	5 year cure	Lost	Dead		
6770	56	M	7		Epidermiod gr. 1–2	10/41	24.48			10.41	+		4,800				+			
6901	55	M	3		Epidermoid gr. 1–2	12/41	34.56			6.42 +	+		3,600	5.42				+	Lymph node metastasis	11/43
7081	58	M	4		Epidermoid gr. 1–2	2/42		8,000							9.42		+			
7150	59	M	7		Epidermoid gr. 1–2	3/42	23										+			
7155	48	F	2	Sharp tooth	Epidermoid gr. 1–2	3/42		+		9.42	+		5,600							
7187	52	M	8		Epidermoid gr. 1–2	3/42	Too advanced for treatment										+			
7486	67	M	10		Epidermoid gr. 3–4	9/42		11,600						3.43		Radio-necrosis	7.45 +			
7694	55	M	4		Epidermoid gr. 1–2	11/42		12,400					6.43						Progression	
7701	53	M	1		Epidermoid gr. 1–2	12/42		5,600					2,000							
7824	56	F	5		Epidermoid gr. 3–4	1/43											8.45 +			
7857	41	M	16	Leukoplakia	Epidermoid gr. 1–2	2/43	11.52													
7867	56	M	24			2/43	Too advanced for treatment											+	Cachexia	5/43
8013	49	M	2		Epidermoid gr. 1–2	4/43	Too advanced for treatment											+	Local recurrence	12/47
8123	63	M	4	Leukoplakia	Epidermoid gr. 1–2	6/43	36.48			9.47	+		4,400				+			
8182	55	M	16		Epidermoid gr. 1–2	7/43	6.48							10.44			+			
8355	68	F	2	Sharp tooth	Epidermoid gr. 1–2	9/43	5.76			+	−						+			
8408	62	M	14	Leukoplakia	Epidermoid gr. 1–2	10/43	22										+			
8502	62	M	9		Epidermoid gr. 1–2	11/43		10,900										+	Pulmonary metastasis	11/44
8639	43	M	24		Epidermoid gr. 1–2	1/49	31.7			+	+		3,550					+	Local recurrence	1/47
8896	51	M	2		Epidermoid gr. 1–2	6/44	16.8			7.44	−			9.46				+	Local recurrence	1/47
8996	51	M	2		Epidermoid gr. 1–2	6/44	16.8			7.44	—		10.46 8,200	8.46			+		1.45 necrosis	
9047	61	M	3		Epidermoid gr. 1–2	7/44		8,000 7,200									+			
9049	67	M	4		Epidermoid gr. 1–2	7/44		7,200									+			
9348	57	F	6		Epidermoid gr. 1–2	11/44	11.52			12.44	−			8.45				+	Local progression	9/45
9431	60	M			Epidermoid gr. 1–2	12/44		9,000												

dissection was either radium in a molded apparatus or roentgen therapy. Radium treatment when expressed in figures means the total amount of millicuries destroyed at a distance of 5 to 6 cm. to the skin surface in seven or eight days. Roentgen therapy is shown in terms of total number of roentgens on the skin surface.

We admit that these treatments were performed in our early cases. At present we are no longer convinced of the value of radiation treatment after a neck dissection. The column on "results" in Table VI is self explanatory, and in the last figures for date of death the first number represents the month and the second one the year.

RESULTS

Of a total of 113 cases, 15 did not receive any treatment because they were too far advanced. Of the remaining 98 cases, there are 37 in which no follow-up has been obtained. There are, therefore, 61 patients whom we have been able to trace. Of these, 5 are alive without evidence of disease at the end of five years (8.1 per cent).

SUMMARY

One hundred and thirteen cases of cancer of the tongue have been analyzed. It is felt that leukoplakia and traumatic irritation by a sharp tooth are the most important predisposing factors to the development of lingual cancer.

Lesions of the anterior two-thirds of the tongue were treated with interstitial radium needles and those of the posterior third with external roentgen irradiation.

Lymph node metastases from cancer of the anterior two-thirds of the tongue were treated by radical neck dissection.

Lymph node metastases were present in 75.2 per cent of all cases.

Prophylactic neck dissection is advised.

The five year cure rate of the 113 cases reviewed is 8.1 per cent.

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Vol. 71, No. 2

EFFECTS OF IRRADIATION ON POST-TONSILLECTOMY PAIN*

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PAIN following tonsillectomy has always been a constant and troublesome complication. Its control during postoperative hospitalization is usually dependent upon the analgesic action of certain alkaloids of opium (morphine, pantopon, narcophine) and thereafter upon the local anesthetic action of such drugs as acetylsalicylic acid, orthoform or anesthesin. Because many diverse types of pain have been found to be relieved by roentgen therapy, an attempt was made to assess the effects of postoperative roentgen therapy on the tonsillar fossae.

Forty adults were subjected to tonsillectomy under local anesthesia. Prior to operation, complicating diseases such as diabetes, cardiovascular disease and endocarditis were ruled out. Each patient received 3 grains of nembutal forty-five minutes before operation. Morphine sulfate and codeine sulfate were used for the symptomatic relief of pain and the total quantity of each drug required for every patient was recorded. The patients were observed in the hospital for twenty-four hours after operation and re-examined on the third, seventh and tenth postoperative days.

Of the 40 patients, 20 consecutive patients were used as a control group: the other group of 20 consecutive patients was given doses of 100 roentgens† postoperatively as follows:

Group 1 (5 patients) received 100 roentgens (in air) delivered through a submental portal to the right tonsillar fossa immediately after operation.

Group 2 (5 patients) received 100 roentgens (in air) delivered through submental portals to each tonsillar fossa immediately after operation.

Group 3 (5 patients) received 100 roentgens (in air) through a submental portal to the right tonsillar fossa two hours after operation.

Group 4 (5 patients) received 100 roentgens (in air) delivered through submental portals to each tonsillar fossa two hours after operation.

In all four groups the following physical factors were employed: 135 kv., 8 ma., 25 cm. skin-target distance, 0.25 mm. Cu plus 1 mm. Al filtration giving a half-value layer of 0.4 mm. Cu, and a cylindrical cone 5 cm. in diameter. It is estimated that on the average the tonsillar fossa lay about 3 cm. from the end of the cone giving a tissue dose of approximately 75 per cent of the air dose.

The criteria for evaluating the post-irradiation effects were as follows:

1. Lateralization of pain.
2. Subjective reaction of the patient.
3. Total quantity of analgesic drugs required.
4. Unusual hemorrhagic effects.
5. Healing time.

The effects of post-tonsillectomy doses of radiation applied to the tonsillar fossae are shown in Table 1.

(1) There was no lateralization of pain to either the treated or the untreated side in those patients receiving unilateral doses of radiation (Groups 1 and 2).

(2) None of the 20 patients receiving postoperative doses of radiation appeared to experience relief of subjective pain. The variations in subjective symptoms failed to

† The dosage of 100 roentgens was selected arbitrarily but was regarded as being sufficient to produce appreciable local effects without inducing serious deleterious action.

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TABLE I

TWENTY PATIENTS RECEIVING IRRADIATION AFTER TONSILLECTOMY

	Lateralization of Pain	Relief of Pain	Hemorrhage		Healing Time	Average Use of Analgesic Drugs Per Patient
			Immediate	Delayed		
Group 1 (5 patients) 100 r (air) to right fossa immediately after operation	0	0	4	0	Normal	Morphine sulfate, gr. ¼ (0.016 gram)
Group 2 (5 patients) 100 r (air) to each fossa immediately after operation	—	0	3	1	Normal	Morphine sulfate, gr. ¼ (0.016 gram)
Group 3 (5 patients) 100 r (air) to right fossa 2 hours after operation	0	0	0	0	Normal	Morphine sulfate, gr. ¼ (0.016 gram)
Group 4 (5 patients) 100 r (air) to each fossa 2 hours after operation	—	0	0	1	Normal	Morphine sulfate, gr. ¼ (0.016 gram)

follow a specific pattern, were comparable to those experienced by the 20 patients who did not receive doses of radiation and could be explained on the basis of individual differences in pain threshold.

(3) The total amount of analgesic drugs and the duration of their administration were approximately the same in the patients receiving postoperative irradiation as in the control group.

(4) In Group 1, one patient developed a fairly active hemorrhage from the treated fossa two hours after irradiation, but was controlled by pressure and chemical cauterization. Three other patients in this group developed slight bleeding from the irradiated side within six hours but the hemorrhage was controlled by pressure alone.

In Group 2, three patients developed bleeding within two hours after irradiation, with evidence of generalized vasodilation and with numerous small bleeding points in each fossa. One of the three patients also experienced slight bleeding on the sixth day. No large vessels were involved in this group and the hemorrhage was controlled in each instance by chemical cauterization.

In Group 3 and Group 4, no immediate bleeding occurred and in only one patient in Group 4 was there delayed bleeding. This occurred on the sixth postoperative day, was slight and ceased spontaneously.

(5) Healing of the fossae appeared to be complete at the end of ten days and the healing time did not differ from that of the patients of the control group.

The experiment was discontinued without using larger doses of radiation or different time intervals when it became evident that no analgesic effects were being obtained.

SUMMARY

1. Twenty patients subjected to tonsillectomy under local anesthesia were given roentgen therapy postoperatively in an attempt to control pain.

2. No significant analgesic effect could be detected.

3. Of ten patients receiving roentgen therapy immediately after tonsillectomy, seven had mild hemorrhagic manifestations; those receiving treatment on one side alone experienced bleeding only on the treated side.

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Vol. 71, No. 2

AN EVALUATION OF THE EFFICIENCY OF VARIOUS INTRAUTERINE RADIUM TECHNIQUES IN THE TREATMENT OF CANCER OF THE CORPUS UTERI*

FACTORS INFLUENCING THE ESTABLISHMENT OF A TREATMENT POLICY

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THE value of preoperative radium therapy in the treatment of endometrial cancer still remains a controversial problem among surgeons. Various results have been reported, most of which indicate preoperative radium to be of real value but others seem to show that it is of questionable or of no value as an adjunct to surgery.

When such diametrically opposite opinions continue to exist regarding a therapeutic agent, some variable in its use must be present to account for this disagreement. In any review of the literature, one is immediately impressed by the wide variation in the methods of radium application, dosage, and duration of treatment used in the management of this disease. Information is often scanty as to the strength of the radium or radon tubes, filtration, and technique utilized.

Dosage is nearly always stated in milligram hours and the results evaluated on this basis apparently on the assumption that such a specification of dosage in itself adequately describes the amount of radiation reaching the tumor. In histopathological studies of uteri removed after preoperative radium therapy, the authors frequently point out that areas of radiation necrosis were present in normal tissue while carcinoma in immediately adjacent or nearby areas was only slightly damaged or that the cancer showed no detrimental effect from a milligram-hour dosage that clearly had damaged the myometrium and its vessels. Such statements are often taken as an indication of the marked radioresistant nature of the tumor when in actuality they merely indicate the marked localized nature of the radiation from the radium sources.

Since the milligram-hour dose in itself does not give one any real information concerning the amount of radiation reaching the tumor cells, such a statement of dosage can have little or no value in studying the biological effect of radium unless it is accompanied by a knowledge of the physical factors used and the geometrical arrangement of the radium in relation to the tumor so that an estimate of the tumor dose in gamma roentgens can be measured or calculated. In fact, it may actually serve to confuse one's colleagues and hinder rather than aid the study and evaluation of radium as a therapeutic agent in the treatment. Much of the controversy that exists at the present time seems to arise from a failure to correlate these technical factors of technique, tumor dose, and treatment time with the results achieved.

It is the purpose of this paper to consider the various methods of radium application which have been proposed or used in the treatment of endometrial cancer; evaluate their relative efficiency, first from a physical analysis of dose distribution, and second from an analysis of reported histopathological or clinical results obtained by the particular technique. It is believed that such an analysis will help to more clearly establish the value of preoperative radium in the treatment of endometrial cancer and

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point out by what technique it should be applied for maximum benefit.

Some of the methods of radium application used in their probable order of efficiency, are: a single radium or radon tube of high milligram strength, a short intrauterine tandem, a long tandem reaching from the external os to the superior wall of the fundus, special applicators such as the Schmitz Y applicator,[34] the Friedman hysterostat[10] Martin's hinged applicators[19] Kaplan's flexible catheter,[17] the Crossen wire technique,[8] and finally, the flexible packing method as advocated by Heyman[15] and adopted in a more simplified form by Nolan and Arneson,[23] Campbell,[6] and Howe and Jennings.[16]

The efficiency of a given radium application depends chiefly upon: the sensitivity of the growth to radium, the proper placing of the radium tubes in the uterine cavity, uniformity of the dose distribution, duration of treatment, and adequate dosage to all of the tumor which requires a close proximity of the radium to the growth, especially the invading portions farthest away fron the radium. Sampson,[31] in 1934, in a careful clinical analysis of the intrauterine tandem, pointed out many factors which make it a rather inefficient method of applying radium in endometrial cancer, except in superficial lesions in small uteri with thin walls where one has reasonable assurance that the radium is in close proximity to the tumor.

The relative inefficiency of the intrauterine tandem as a method of applying radium in endometrial cancer also becomes readily apparent when one studies the dose distribution about such an applicator. The dose pattern

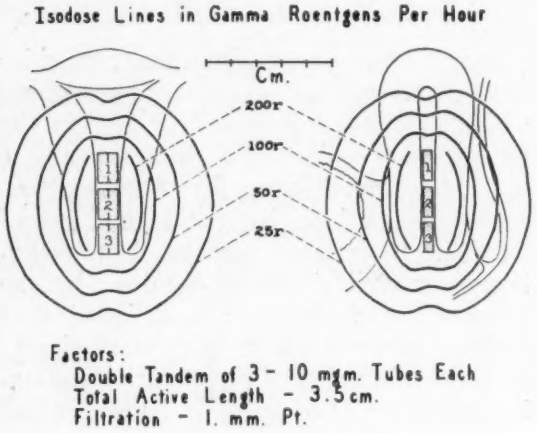

FIG. 1. Diagram of radiation distribution about a short intrauterine tandem.

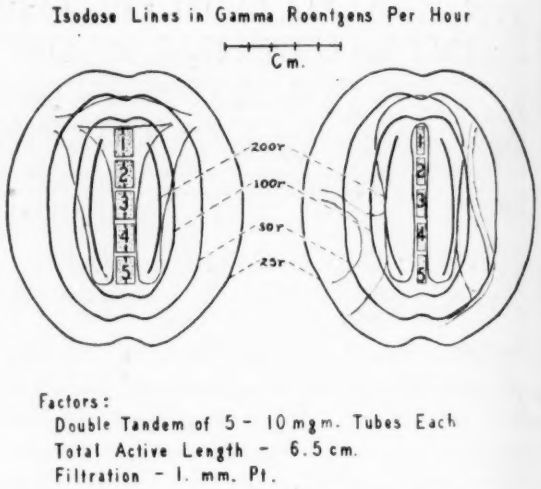

FIG. 2. Diagram of radiation distribution about a long intrauterine tandem extending from the external os to the superior wall of the uterus.

about a short and a long intrauterine tandem is shown in Figures 1 and 2. These diagrams were prepared for a normal sized uterus taken as 8 by 5 by 3.5 cm. in dimension and in standard relationship to the other pelvic organs. The radiation sources used were from our available radium supply and consist of radium tubes of 12 mm. external length containing removable 10 mg. cells of 7 mm. active length with a total filtration of 1 mm. platinum.

The short tandem is 4 cm. in external length, 3.5 cm. over-all active length, and contains 60 mg. of radium with 1 millimeter of platinum filtration. The desired tandem is made up by placing three of the small 10 mg. radium sources in each of two short pieces of rubber tubing of 1 mm. wall thickness and using them in a double tandem arrangement.

The long tandem is 7 cm. in external length, 6.5 cm. over-all active length, and contains 100 mg. of radium with 1 mm. of platinum filtration. This requires ten of our 10 mg. tubes in a double tandem arragement.

The dose per hour was calculated at many points about the uterus by using Quimby's[30] table for linear radium sources after correction for the additional filtration and the selected 200 r, 100 r, 50 r, and 25 r per hour isodose curves drawn in. To determine the total dose delivered in any particular application, it is only necessary to multiply the dose rate per hour by the duration of the treatment in hours.

From a study of these diagrams, it is readily apparent that, with a short tandem, most of

Fig. 3. Perforation of the uterus during an intrauterine radium application.

the radiation is confined to the lower half of the uterus. With a long intrauterine tandem, extending from the external os to the superior wall of the uterus, the dose pattern is elongated and the uniformity of the dose to the uterus considerably improved. Uniformity of the dose distribution is obviously the most important factor in any comparison of radium techniques, for, in any radium application, the problem is always one of trying to deliver a minimum dose high enough to be lethal to all of the tumor cells while at the same time keeping the maximum dose below that which will destroy normal tissue.

In an effort to improve the dose distribution, Crossen[8] developed a new technique in which he utilized three separate tandems each consisting of two radium tubes which were inserted

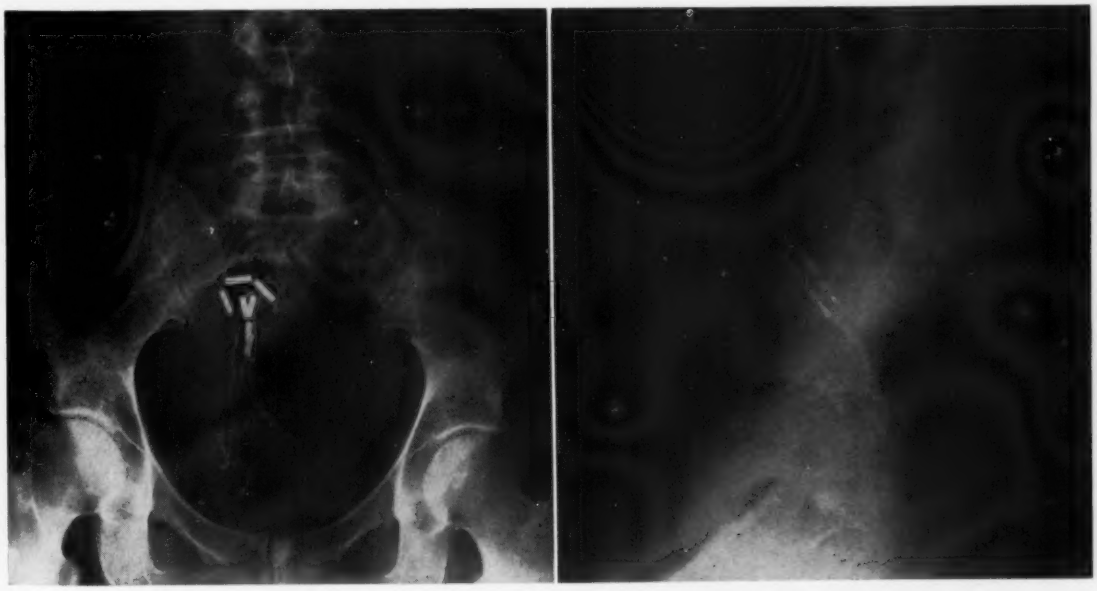

Fig. 4. Roentgenograms of the first of two radium applications in a patient with inoperable carcinoma of the fundus.

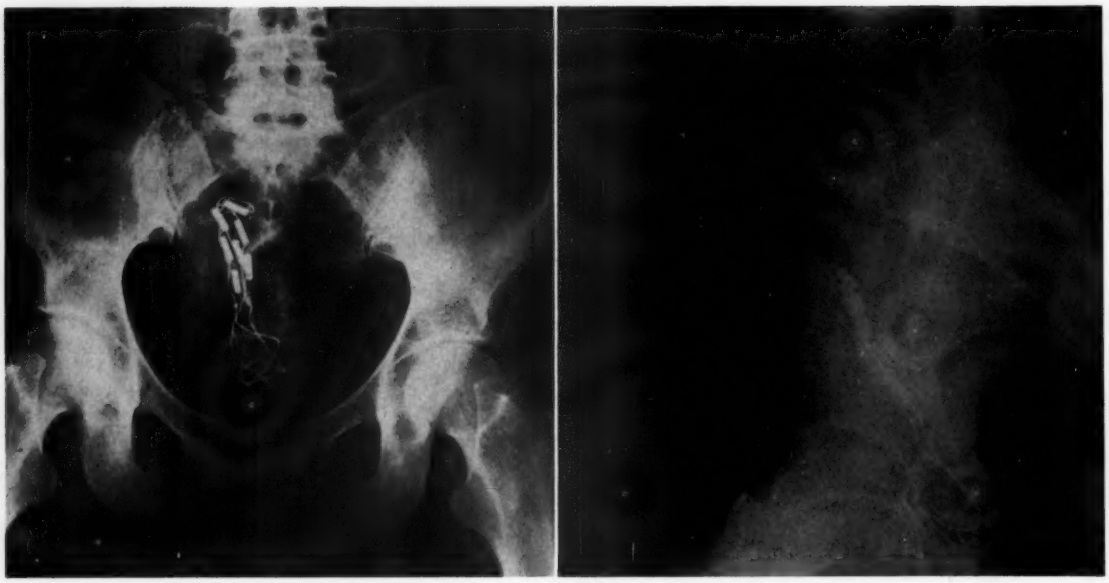

FIG. 5. Roentgenograms of the second radium application in a patient with inoperable carcinoma of the fundus.

so that one tandem lay adjacent to each lateral wall with a central tandem in the middle of the uterus. Payne,[29] in an attempt to improve on this technique, added a third radium tube to one of these tandems which is inserted first and an effort made to manipulate this tandem so that one of the radium tubes lies along the superior wall of the uterus. The various tandems contain 30, 20 and 20 mg. of radium respectively. This radium is left in place for fifty to sixty-five hours, or 3,500 to 4,550 mg. hr. in the operable patients, and the uterus removed six weeks later. In the inoperable patients, a second similar application is made in four weeks for a total of 7,000 mg. hr. Roentgenograms are taken after each application to determine whether the technique has been properly carried out and to enable one to make an estimate of the tissue roentgen dose and its distribution. Occasionally a uterus may be perforated during the radium insertion and this is also readily revealed by the roentgenograms, as shown in Figure 3. When such perforations occur, the radium is immediately removed and damage to the intestines prevented.

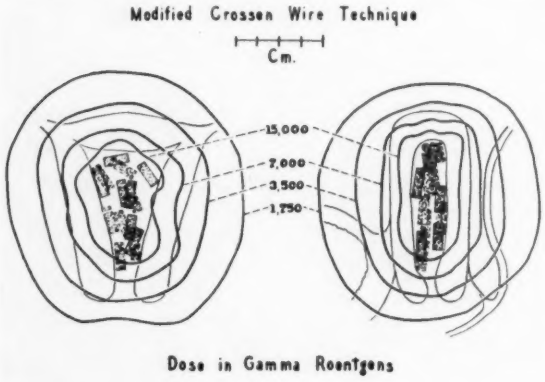
Modified Crossen Wire Technique
Cm.
15,000
7,000
3,500
1,750
Dose in Gamma Roentgens
Dosage:
First Treatment - 7 x (10 mgm) x 50 Hours = 3500 mgm-hrs.
Second Treatment - 7 x (10 mgm) x 50 Hours = 3500 mgm-hrs.
(Four weeks later)
Total Treatment - 7000 mgm-hrs.

FIG. 6. Radiation distribution about the combined radium applicators shown in Figures 4 and 5.

The roentgenograms taken after two applications of radium in an inoperable patient are shown in Figures 4 and 5. The dose pattern for the combined radium application is shown in Figure 6. Considering 7,000 gamma roentgens when given in ten to twenty days as a cancerocidal dose, it can be seen from this diagram that most of the uterus is adequately treated except for small portions of the cornu and most of the cervix. This, however, is only obtained by treating a rather large volume of uterine wall up to or beyond 15,000 gamma roentgens.

Schmitz[34] developed a special Y-shaped applicator which improved the dose distribution in the cornu; Friedman[10] proposed a new

device termed a hysterostat which improved the dose especially along the superior wall and in the cornu of the uterus; Kaplan[17] introduced small radium capsules in a long catheter for the purpose of improving the flexibility of radium application; and Martin[19] designed separate hinged applicators which could be placed at any angle in the upper uterine cavity and held in place. These represent a few devices suggested for improving the radiation distribution and flexibility of the radium applications in the uterine cavity. In general, all of these devices tend to improve the radiation distribution over that of the uterine tandem but leave something still to be desired in regard to adaptability to varying sizes and shapes of uteri and some uncertainty as to the actual relationship of the radium to the tumor growth.

Heyman,[15] recognizing the inadequacies of the tandem technique, developed a packing method in 1935 which has been used routinely in treatment and adopted completely, or with slight modification, in many other European clinics. The basic principle of this technique is to pack the uterus full of uniform radiation sources small enough to permit contact irradiation of the entire uterine wall, including the cornu. Radium tubes containing 8 mg. of radium with an active length of 15 mm., external length of 20 mm., and a wall thickness of 0.6 mm. platinum are used. These tubes can be fitted into four different sizes of additional filters differing in respect to their external diameter which is 7.8 mm., 9.8 mm., 11.8 mm., and 13.8 mm. respectively. The variation of the diameter is achieved by varying the air space between the external wall of stainless steel and the inner wall of lead. The total filtration is equivalent to 1.5 mm. of platinum. Special instruments were developed for inserting these radium applicators into the uterus. The uterus is packed with whatever size is considered suitable with an optimum of ten applicators per uterus. On the basis of previous empirical experience, Heyman considers a dose of 1,500 mg. hr. given twice at three week intervals as the most suitable when applying ten of the No. 1 applicators, each containing 8 mg. of radium. Measurements were made about several experimental phantom uteri constructed of canvas bags of varying sizes in order to determine the intensity and uniformity of the dose assuming a uterine wall of 1.5 cm. thickness.

The average dose about the external surface of the uterine wall of 1.5 cm. thickness for the above technique is 1,800 gamma roentgens. This appears to be a very conservative dose and could be increased without producing any severe radiation necrosis. However, Heyman feels that it is adequate in his own experience and such an increase therefore not warranted. Tables were constructed from these measurements which give the time of treatment necessary to deliver this dosage, regardless of the number and size of applicators used. Individual total dosages in milligram hours may vary from 1,800 to 4,000 mg. hr. One of the uterine treatments is combined with radium treatment to the vaginal vault, and supplementary roentgen therapy is used in the more advanced cases where the tumor has spread outside of the uterus.

This packing technique was used in all but the very small uteri where a radium tandem was still utilized. After treating a series of patients, Heyman[14] found the results with the packing technique to be so superior to the tandem that he has now developed two smaller capsules which make the method adaptable to all uteri, regardless of size.

In adenocarcinoma of the uterus 7,000 gamma roentgens, when delivered in from two to three weeks, is usually considered as the minimum dose necessary to destroy the cancer cells, and 15,000 gamma roentgens as the maximum dose which should not be exceeded if general tissue necrosis is to be avoided. The high dosage gradient from a radium source, *i.e.*, the rapid decrease in dosage with distance makes it often very difficult to deliver an adequate dose to the farthest tumor cells without producing a large amount of necrosis in the tissue immediately adjacent to the radium. Any extensive necrosis of normal tissues in the tumor bed can result in unrestrained growth of the cancer cells and is perhaps as equally undesirable as inadequate dosage. Paterson[28] and Tod and Meredith[40] have referred to this as a "supralethal effect." Therefore a technique cannot be considered as satisfactory unless the ratio between the maximum and minimum gamma roentgen dose along the external surface of the uterus does not exceed a factor of 15,000/7,000, or 2.14.

The ratio between the maximum and minimum gamma roentgen dose per hour at selected points about the external surface of a normal-sized uterus for several techniques are shown in the last column of Table 1. The diagram and selected points are the same as those used by

TABLE I

A STUDY OF THE DOSE DISTRIBUTION IN GAMMA ROENTGENS PER HOUR AT SELECTED POINTS ABOUT THE EXTERNAL WALL OF THE UTERUS FOR SEVERAL INTRAUTERINE RADIUM TECHNIQUES

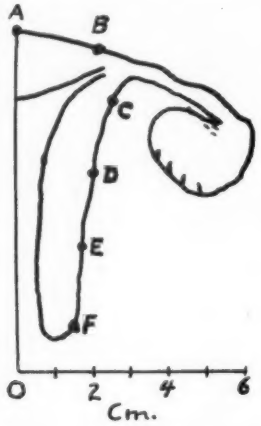

Diagram Showing Selected Points Around the Uterus

Intrauterine Radium Technique		Dose in Gamma Roentgens per hour at Selected Points						Ratio Maximum to Minimum Dose
Type of application	Total radium (mg.)	A	B	C	D	E	F	
Short tandem (3.5 cm.)*	60	12	14	21	60	121	100	10.0
Long tandem (6.5 cm.)*	100	32	42	66	131	150	108	4.7
Modified Crossen wires	70	50	35	45	60	110	35	3.1
Y applicator	125	87	79	250	206	338	213	4.3
Hysterostat	125	125	150	500	300	250	213	4.0
Multiple capsules	87.5	79	79	180	210	210	96	2.7
Multiple capsules	137.5	151	151	330	330	357	261	2.4
Heyman packing method	96	46	45	50	58	51	41	1.4

* Active length.

Nolan and Natoli[24] in a previous similar study.

The values of radiation dosage listed in Table 1 for the short intrauterine tandem, long intrauterine tandem, and modified Crossen wire technique were determined by mathematical calculation for the techniques as previously described. The figures for a Y applicator, hysterostat and two packing methods were taken from data published by Nolan and Natoli[24] as obtained by their film method of dosimetry, and those for one type of Heyman's packing method were estimated from the data published by Heyman, Reuterwall and Benner[15] for an experimental measurement about a phantom uterus using small ionization chambers.

A study of the ratio between the maximum and minimum gamma roentgen doses delivered by these various techniques shows at once that this ratio does not approach the limiting factor of 2.14 except in the packing techniques. Thus, it is readily apparent that a minimum dose approaching 7,000 gamma roentgens can only be delivered by the packing methods without exceeding normal tissue tolerance.

The efficiency of various radium techniques can also be determined by a careful histopathologic study of removed uteri following combined radiation therapy and surgery. A few such studies have been made by several authors as shown in Table II. Some of these authors gave a short course of roentgen therapy along with the radium treatment, as indicated in the table. From this table it can be seen that the re-

TABLE II

A STUDY OF THE REPORTED INCIDENCE OF RESIDUAL TUMOR IN OPERATIVE SPECIMENS IN RELATION TO THE TECHNIQUE OF RADIUM APPLICATION AND DOSAGE USED IN THE TREATMENT

Seq. No.	Name of Author	Radium Technique	Radium Dosage mc. hr. or mg. hr.	Preliminary Roentgen Therapy (tissue roentgens)	Interval between Irradiation and Surgery (weeks)	No. of Cases	Complete Regression	Residual Cancer	Per Cent with Residual Cancer
1	Donovan and Warren[9]	Tandem (radon)	1,700–3,000	None	6–10	13	2	11	85
			3,000–4,500	None	6–10	33	3	30	91
2	Healy and Brown[12]	Tandem (radon)	1,200–2,700	None	6–10	24	3	21	88
			3,000–3,300	None	6–10	25	13	12	48
			3,400–4,000	None	6–10	20	12	8	40
3	Smith[37]	Tandem	2,400–3,600	(?) few pts.	4–7	24	4	20	83
4	Arneson, Stanbro and Nolan[2]	Tandem	3,000–5,000	1,200–1,600	1–6	13	3	10	77
5	Palmer and associates[27]	Tandem	4,500–9,000	None	6	86			69.7
6	Brindley[4]	Tandem	800–4,500	None	6	34	16	18	55.8
7	Scheffey *et al*.[32]	Tandem	2,000–5,000	None	8–10	30	15	15	50
8	Taylor and Becker[39]	Tandem	Av. 3,600	(?) few pts.	6	119	60	59	49.6
9	Corscaden[7]	Tandem or spring wire device (7 tubes)	1,200–5,000	None	1–20	70	17	53	75.7
10	Stowe[38]	Tandem	2,000–4,900	<2,190	4–6	7	4	3	43
		Jointed tandem applicator	Less than 4,500	<2,190	4–6	6	2	4	67
			More than 4,500	>2,190	4–6	40	20	20	50
11	Schmitz, Sheehan and Towne[25]	Y applicator	Less than 6,000	>4,000	?	5	0	5	100
			6,000 —	4,000	12–34	6	5	1	16.5
12	Friedman[10]	Hysterostat	4,000–8,000	—	?	8	7	1	12.5
13	Gray, Friedman and Randall[11]	Hysterostat	6,000–12,000	(?) 1 pt.	7–24	7	1	6	85
14	Arneson, Stanbro and Nolan[2]	Packing method	3,500–7,000	1,200–1,600	1–6	19	1	5	26.3

ported incidence of residual tumor in operative specimens following radium therapy varies from 12 to 91 per cent. There was usually very little attempt made by the authors to correlate such histopathologic studies with the technique of radium application or to obtain roentgenographic proof that the technique was properly carried out. A correlation of histopathologic findings with dosage in milligram hours was usually made, but the inadequacy of this method of stating dosage as a basis for planning techniques or evaluating therapeutic results has already been emphasized.

Donovan and Warren,[9] in a histopathologic study of the irradiated uteri of 46 cases following removal six weeks after radon therapy, report residual tumor as present in 41 of this group (89 per cent), one of the highest incidences noted in the literature. According to these authors the radon was applied by means of various types of single applicators of a length conforming to that of the uterine canal. The dosage varied from 1,700 to 4,500 mc. hr. No statement is given as to the strength of the individual radon sources, filtration, or duration of treatment, nor is any attempt made to ex-

plain why such a wide variation in the millicurie-hour dosage was used.

Healy and Brown[12] found residual tumor in only 60 per cent of the removed uteri of 69 patients treated by means of a radon tandem, which compares rather favorably with the results reported by Corscaden,[7] Arneson *et al.*,[2] and others following a radium tandem. The lowest incidence of residual tumor following the use of intrauterine tandem applicators is 50 per cent as reported by Scheffey *et al.*[32] in a series of 30 patients, and Taylor and Becker[39] in 119 patients.

Stowe,[38] using a special jointed tandem applicator, reported residual tumor in 20 (50 per cent) of 40 uteri studied histopathologically upon removal five weeks after treatment, with a dosage of over 4,000 mg. hr. Some of these patients received supplementary roentgen therapy. He includes a review of the literature on histopathologic studies where either roentgen therapy, radium or both were used in treatment. In four reports where roentgen therapy was utilized, he noted that a measurement of the amount of radiation delivered to the tumor area received attention in only one of the discussions. He states that the others contented themselves with mentioning the use of roentgen rays or stating that a given number of roentgens were delivered without reference to the point at which the measurement was made.

In his own paper Stowe[38] gives the calculated tumor roentgen dose delivered by roentgen radiation but stated the radium dosage in milligram hours, failing to recognize that an evaluation of the tissue roentgens delivered by radium is equally as important and necessary as in roentgen therapy.

Using a special Y-shaped applicator, Schmitz and his co-workers[35] reported residual tumor in 6 (54 per cent) of 11 patients. However, none of the 6 patients with residual tumor received what the authors considered as adequate therapy, which is defined as 6,000 milligram hours of radium given in three doses of 2,000 milligram hours, each at intervals of one week by means of a Y applicator and followed by deep roentgen therapy to a tumor dose of 4,000 roentgens in twenty-eight days.

Friedman,[10] in describing a new applicator termed a hysterostat, reported eradication of tumor in 7 of 8 uteri removed at operation four to six weeks after receiving at least 4,000 mg. hr. of radium. In a later series, Gray, Friedman and Randall,[11] using this same hysterostat, found tumor growth remaining in 6 of 7 patients. Combining the two reports, the incidence of residual tumor following the use of this hysterostat is 47 per cent (7 of 15 patients))

Arneson, Stanbro and Nolan,[2] using a packing method of applying radium in the uterus, found residual tumor in only 26.3 per cent of 19 uteri removed from one to six weeks after radiation treatment.

Thus on the basis of these histopathological studies, it would appear that the efficiency of the various special applicators is slightly better than that of the intrauterine tandem in eradicating fundal carcinoma, but a significant improvement is only evident when a packing method of application is used.

A third method of determining the value of radium therapy in the treatment of endometrial carcinoma is through an analysis of the five year survival rates in the clinically or technically operable patients treated by surgery or radiation alone, or combined radiation and surgery.

In order to obtain a sufficiently large series of patients in any one of these categories, it is necessary to assemble the statistics of a number of authors, as shown in Table III. The average five year survival rate in clinically operable patients is found to be 55.3 per cent in 715 patients for surgery alone, and 57.1 per cent in 361 patients for combined radiation and surgery. In clinically or technically operable patients, the average survival rate for radiation alone is 52.5 per cent in 245 patients.

The collected statistics, as assembled by Arneson in 1936 from a somewhat different group of reports, are also shown in Table III. He found the average five year survival rate in clinically operable patients to be 57 per cent in 927 patients for surgery alone, and 60 per cent in 91 patients treated by combined radiation and surgery. Clinically or technically operable patients treated by radiation alone showed an average five year survival of 53 per cent in 473 patients.

When results are analyzed in this manner, there appears to be very little difference in the five year survival rates for the three methods of treatment, and it is not difficult to understand why the question frequently arises among various authors as to the value or necessity of the combined treatment. It should be noted that most of these writers reported results accumulated over a period of twenty years or more, and hence they are not of much help in

TABLE III

FIVE YEAR SURVIVAL RATE IN ENDOMETRIAL CARCINOMA ACCORDING TO THE METHOD OF TREATMENT

Name of Author	Operation Alone			Irradiation Alone; Technically Operable Cases			Irradiation and Operation			Irradiation Alone; All Cases		
	Cases treated	Alive 5 yr.	Per cent	Cases treated	Alive 5 yr.	Per cent	Cases treated	Alive 5 yr.	Per cent	Cases treated	Alive 5 yr.	Per cent
Arneson[1] (1936 report)	20	13	65	7	4	57	10	9	90	18	5	28
Bowing and Fricke[9] (1925–1935)				44	29	66				109	43	39
Brindley[4] (1921–1940)							24	19	79.1	31	13	41.9
Burnam[5] (up to 1925)	6	3	50	27	15	55	9	5	55.0	57	19	33
Healy and Brown[12] (1918–1932)							93	52	55	96	37	39
Masson[18] (1916–1927)	331	193	58.3							161	32	20
Morton[20] (1916–1917)	19	12					18	12	66.6	24	9	37.5
Murphy[21] (up to 1933)				58	23	39.6				77	25	32.5
Newell and Crossen[22] (1921–1929)	20	13	65				23	14	60.9	13	2	15
Norris and Dunne[26] (1900–1935)	115	55	47.8							89	39	43.8
Scheffey *et al.*[33] (1921–1940)	12	5	41.6				37	17	46.0	55	22	41.8
Smith[36] (up to 1927)	152	78	51									
Taylor and Becker[39] (1926–1940)	19	11	58	109	57	52	126	66	52.0	213	70	33
Ward and Sackett[41] (1919–1931)	21	13	61.9				21	12	57.1	59	21	35.6
TOTAL	715	396	55.3	245	128	52.2	361	206	57.1	1,002	337	33.6
Collected statistics various authors by Arneson[1] (1936)	927	530	57.0	473	250	53.0	91	55	60.0	998	372	37.0

evaluating present day techniques of either surgery or irradiation. This is particularly true in regard to radium therapy since wide variations were present in the method of its application, dosage, and duration of treatment.

These collected results do, however, seem to indicate that where the radium is applied on a relatively unplanned, unscientific basis, some doubt as to its value as an adjunct to surgery in the operable patient might be justified. A real effort must therefore be made to apply radium by the most efficient method in adequate dosage if one is to obtain a significant improvement in results. The studies made by Heyman, and his associates,[13,14,15] and Arneson *et al.*,[2] shown in Table IV, serve to re-emphasize this point. It can be seen from their results that where a packing method was used there was a significant improvement for radiotherapy alone or combined radiotherapy and surgery in the clinically operable patient over that for surgery alone in collected statistics. Using radiotherapy alone with operation only in cases of radiation failure, Heyman [13] found 115 of 153 patients (75 per cent) alive and free of disease after a period of five years.

Since from 5 to 10 per cent of patients with uterine carcinoma, according to the reports of Corscaden,[7] Sampson,[31] and Donovan and Warren,[9] may have involvement of the tubes or ovaries not detectable clinically and outside of the region adequately treated by radium this would suggest that it should be possible to obtain a five year survival rate of from 80 to 85 per cent by a combined packing method followed by surgery in all operable cases. Arneson's[2] preliminary report of a 79 per cent five year survival in a small series of 19 consecutive patients treated in this manner suggest that this goal might well be attained.

A comparison of the five year survival rates in all patients treated by radiation alone as

TABLE IV

FIVE YEAR SURVIVAL RATE IN ENDOMETRIAL CARCINOMA FOLLOWING IRRADIATION BY A RADIUM PACKING TECHNIQUE WITH OR WITHOUT SUBSEQUENT HYSTERECTOMY

	Irradiation Alone Clinically Operable			Irradiation Technically Operable			Irradiation Alone All Cases			Irradiation plus Operation All Cases		
	Cases	5 yr. cures	Per cent	Cases	5 yr. cures	Per cent	Cases	5 yr. cures	Per cent	Cases	5 yr. cures	Per cent
Heyman *et al.*[13,14,15]												
Tandem method	151	75	50	144	45	32	327	131	40	354*	158	45
Packing method	153	102	67	135	69	51	294	183	62	316*	205	65
Arneson, Stanbro and Nolan[2]												
Tandem method							18†	4	22	13†	7	54
Packing method							25†	8	32	19†	15	79

* Patients treated by irradiation alone with hysterectomy only after irradiation failure.
† Patients also received a preliminary course of roentgen therapy to a tumor dose of approximately 1,600 roentgens.

assembled in the last column of Tables III and IV also shows a significant improvement in the results following the use of a packing method. It should be noted, however, that Heyman's results in this group, which include the inoperable patients, cannot be compared with those of most other authors, because of a different method of classification. He does not classify a case as cancer of the fundus unless it can be definitely established as arising from the fundus. Patients with coincident cancer of both the cervix and fundus are classified as "cancer corporis et colli uteri," those with coincident cancer of the uterus and ovaries, as "cancer uteri et ovarii," and those with coincident involvement of the uterus and several pelvic organs as "cancer pelvis." At least some of these patients would be included under cancer of the fundus by other investigators.

A corollary to this third method of studying the value of radiation therapy in operable patients would be to compare the five year survival rate in patients with or without residual tumor in the operative specimen after preoperative radiation therapy as shown in Table V.

Arneson and his associates[2] and Taylor and Becker[39] report that the five year survival rate was almost twice as good in those patients in whom the tumor was completely destroyed by the preoperative radium therapy.

DISCUSSION

Though radium has been used for many years in the treatment of endometrial cancer, there still remains some controversy among surgeons as to its value as a preoperative measure in the clinically operable patient. Much of this controversy appears to arise from the wide variations

TABLE V

CORRELATION OF PERSISTENCE OF TUMOR IN OPERATIVE SPECIMENS WITH THE METHOD OF RADIUM TREATMENT, RADIUM DOSAGE, AND FIVE YEAR END RESULTS

Name of Author	Radium Technique	Radium Dosage mg. hr.	Total Number of Patients	Persistent Tumor			Unidentified Tumor		
				No. of patients	Per cent of total	Per cent five year results	No. of patients	Per cent of total	Per cent five year results
Arneson, Stanbro and Nolan[2]	Tandem	3,000–5,000	13	10	77	40	3	23	100
	Packing	3,500–7,000	19	5	26	60	14	74	85
Taylor and Becker[39]	Tandem	Av. 3,600	119	59	49.6	44	60	50.4	74

in the methods of radium application, dosage, and treatment time, and the difficulties encountered in trying to evaluate the results on the basis of the amount of radiation delivered in milligram hours when the exact location, size, and extent of the lesion and its relationship to the radium are unknown.

Since it is almost impossible in many cases to determine the location and extent of the tumor, one must therefore utilize a radium technique which will irradiate the entire uterine cavity as uniformly as possible in order to insure the maximum possible biological effect of the radium on the tumor cells. Such a technique must also be adaptable to varying sizes and shapes of uteri.

From a study of the dose distribution about various types of applicators, it has been shown that a satisfactory uniformity of the radiation distribution can only be obtained by means of a radium packing technique. A review of the histopathological studies reported in the literature indicates that as the uniformity of dose for the radium application increases, a corresponding decrease in the incidence of residual tumor in the operative specimen is noted. Using a packing technique in combination with surgery in a small group of 19 patients, Arneson, Stanbro and Nolan[2] found residual tumor in only 25 per cent of the operative specimens.

Studies of the five year survival rate in patients treated by combined radiation and surgery seem to indicate that where the packing method is used, this combined method of treatment can be expected to yield better results than surgery alone in clinically operable patients.

The most frequent sites of recurrence following hysterectomy, according to the reports of Healy and Brown,[12] and Brindley,[4] are in the vagina, vaginal cuff or abdominal wound. For this reason a vaginal radium application, as advocated by Heyman and associates,[15] should be used in conjunction with packing of the uterus in order to insure an adequate dose to the vagina and prevent spread of the tumor at operation.

In any analysis of a radium application, it is also important to recognize its limitations. Nolan and Natoli,[24] by the film method of dosimetry, have clearly shown that a cancerocidal dose cannot be delivered to the adnexa or more lateral portions of the parametria even with the best packing techniques.

The presence of submucosal fibroids, large fungating lesions, and marked thickening of the uterine wall due to deep infiltration may in some cases prevent adequate irradiation of the farthest tumor cells, even though the tumor is still confined to the uterus. Since one or more of these conditions may be present and sometimes not be detectable clinically, a panhysterectomy will be required in all operable patients to give these patients a maximum chance for cure.

On the basis of this study, we, in cooperation with the Staff of the Department of Obstetrics and Gynecology of the Hospital of the University of Pennsylvania, and the Gynecologic Staff of the Jeanes Hospital, are attempting to develop a treatment policy in endometrial carcinoma which might be outlined somewhat as follows:

1. All patients with endometrial carcinoma will be classified according to whether they are clinically operable, technically operable, or inoperable.

2. A radium packing technique and intravaginal radium application similar to that advocated by Heyman and his associates will be used in all patients.

3. Roentgenograms will be made of each radium application to make sure the technique has been properly carried out and to reveal any distortions of the uterine cavity that may prevent adequate irradiation of the tumor growth.

4. The radium treatment will be followed in six weeks by a panhysterectomy, whenever possible, in all clinically operable patients.

5. Careful histopathologic studies of the operative specimens will be made to determine the presence or absence of residual tumor. These findings will be correlated

with the distribution of the radium in the uterus, as revealed by the roentgenograms, and the amount of radiation administered to the uterine cavity in gamma roentgens. These data will also be used as a guide in establishing the amount of radiation that may be required to destroy endometrial carcinoma.

6. When, either at the time of operation or after histopathological study, it is believed that all of the tumor growth has not been removed, postoperative roentgen therapy will be given.

7. In the technically inoperable or advanced cases, the radium treatment will be followed by roentgen therapy to the adnexa and parametria. If the roentgenograms reveal marked distortion of the uterine cavity so as to leave some doubt as to the adequacy of the radium distribution and dosage to the tumor, the roentgen therapy will be directed so as to include the uterine cavity in the treatment.

8. The radiation treatment in the technically inoperable or advanced cases will be followed by uterine curettement in three to six months to determine the presence or absence of residual tumor. Should residual tumor be found during this follow-up study the patient will be re-evaluated from the standpoint of surgery or given further radium or roentgen therapy after due consideration of the risks attendant with each procedure and the general prognosis of the patient.

It is believed that if such a carefully outlined plan of treatment is followed, the results will be improved and the value and indications for radium therapy in this disease more clearly established.

SUMMARY

1. An attempt has been made to study the relative efficiency of various radium applicators which have been proposed or used in the treatment of endometrial cancer—first, from the standpoint of uniformity of dose distribution, and second, from an analysis of the reported histopathological and clinical results obtained by the particular technique.

2. Studies of the dose distribution about eight different types of radium applicators proposed or used in the treatment of endometrial cancer show that a satisfactory uniformity of dosage about the external wall of the uterus can only be obtained by a uterine packing method.

3. The literature on histopathological studies made on removed uteri after preoperative radium therapy has been reviewed. The reported incidence of residual tumor in operative specimens varied from 50 to 91 per cent when an intrauterine tandem was used; from 47 to 54 per cent following the use of various special applicators, and decreased to 25 per cent following the use of a packing technique. Such studies, therefore, indicate that the incidence of residual tumor can be expected to decrease as the uniformity of the dosage for the radium application improves.

4. Studies of the five year survival rate in clinically or technically operable patients, as assembled from the reported results of many authors, show only a slight difference between the results for surgery or irradiation alone or combined irradiation and surgery. Many factors such as case selection, completeness of follow-up, and variations in surgical and radium techniques are present in such assembled data which make them unreliable in studying the value of a treatment agent. These collected statistics nevertheless do seem to suggest that where the radium is applied on a relatively unplanned, unscientific basis, some doubt as to its value as an adjunct to surgery in the operable patient might be justified.

5. The more recent results, as reported by Heyman and Arneson, clearly demonstrate that where the radium treatment is carefully planned and applied by the most efficient method in a flexible packing technique, a significant improvement in the five year survival rate can be obtained with or without subsequent panhysterectomy. Heyman reports 115 patients (75 per cent) alive and free of disease after a period

of five years in a group of 153 clinically operable patients treated by radium therapy followed by surgery only in cases of irradiation failure. Sixty-seven per cent of these patients were cured by irradiation alone.

CONCLUSION

On the basis of this study, we believe the best treatment policy in endometrial carcinoma should include intracavitary radium therapy by a packing technique combined with an intravaginal radium application and followed in four to six weeks by a panhysterectomy in all operable patients. In the technically inoperable and advanced cases this intracavitary and intravaginal radium therapy should be followed in four to six weeks by small field beam-directed roentgen therapy to the adnexa and parametria.

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A FLEXIBLE RUBBER APPLICATOR WITH A POSITIVE SPREAD FOR RADIUM TREATMENT OF CANCER OF THE UTERINE CERVIX*

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IN PRESENTING another applicator designed for the treatment of cancer of the uterine cervix, a statement of our aims as well as our accomplishments would seem to be in order. Concepts of the treatment of this condition have been broadened and clarified in the past few years by the realization that, while adequate dosage to the local lesion is obtained by almost any system of radium application, the dose in the parametrial tissues is all too frequently an unknown quantity that does not control malignant extensions into this area.

This fact has been emphasized recently by the observations of Kimbrough,[15] Meigs,[16,17] Morton,[19] and others, who have been using the surgical approach in selected cases. All of them have found pelvic lymph nodes with uncontrolled metastases in cases that have had "adequate" radiation therapy. Many observers have expressed doubt as to the possibility of control of metastasis to pelvic lymph nodes by irradiation methods. However, Morton[19] offers some encouragement. He says, "For years, evidence of the effectiveness of irradiation upon glandular metastases has been lacking." In a series in which he tried Taussig's idea of lymphadenectomy "we believe that we have learned something of interest and importance. . . ." "Of 51 cases in which the patients had received no preoperative roentgen therapy, regional lymph node metastasis was found in 18, or 35.3 per cent, while of 35 cases in which full roentgen irradiation had been given preoperatively, glandular involvement was found in only 4, or 11.4 per cent. Furthermore there were many more clinically advanced cases in the latter group than in the former." This evidence that irradiation reduces lymph node involvement to a 1 to 3 ratio compared with untreated cases should serve as a new stimulant to those of us who feel that irradiation methods can and should be improved.

We share the feeling of others that most of our failures are the result of improper placement of radium sources and/or failure to keep them in the position in which they were placed during the treatment time. It is the purpose of this presentation to offer a practical instrument that will overcome this and other deficiencies of many techniques of applying intracavitary radium. We also present a system of computing and recording the depth dose, in an effort to correct the inaccuracies that are inherent in methods of evaluating and results on the basis of milligram hours of radium, where we hope it was, instead of gamma roentgens actually delivered where we want them to be.

The importance of the parametrial tissues in the successful treatment of carcinoma of the cervix was emphasized by the work of Tod[25,26,27] and Meredith.[18] They directed attention to the fact that while tumors involve all parts of the cervix, the predominant line of spread is lateral through the paracervical tissues, into the parametrium. A tumor may extend up into the uterus or down into the vagina and over the vault, but rarely, except in very advanced cases, does it extend forward into the bladder or back into the rectum. Tod adds, "This combination of circumstances calls for the creation of a field of radiation of a flattened trefoil shape, maximum along the natural lines of spread and minimal in the direction of the bladder and rectum."

To properly evaluate any system of irradiating these areas they found it neces-

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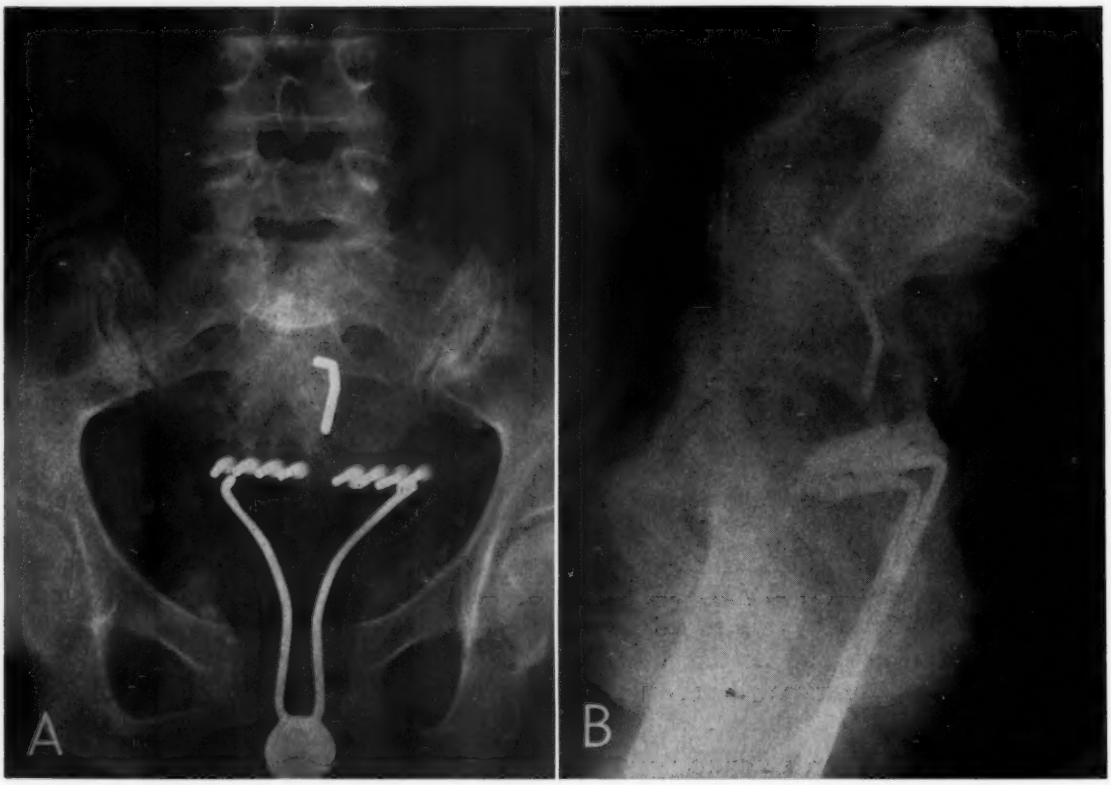

FIG. 1. Anteroposterior (*A*) and lateral (*B*) roentgenograms with applicator in situ. In this case there is a 6 cm. distance between the end capsules. Note vagina distended with packing.

sary to choose points at which intensity could be measured, two points that are "anatomically comparable" from case to case. To quote Meredith:[18] "Our choice of point was guided by the work of T. F. Todd, which showed that the initial lesion of radiation necrosis is due ordinarily to high dosage in the region where the uterine blood vessels are crossed by the ureter. This region we have called the paracervical triangle. Since we may regard the tolerance of this zone as a limiting factor in the irradiation of carcinoma of the uterine cervix, it seemed reasonable to choose a point there for dosage specification. This point, designated as A, is 2 cm. lateral to the center of the canal of the uterus and 2 cm. from the mucosa of the lateral fornix in the plane of the uterus. Because we wanted some idea of the 'throw' of dose toward the pelvis, we calculated the dose at a second point, B, which is at the same level as A but 5 cm. out. Point B is sufficiently near the obturator node to give a reasonable idea of the dose there." It has become common practice to measure the dose at a third point, midway between A and B, that is, 3.5 cm. lateral to the center of the uterine canal, which we will designate as point Y.

In shifting our primary attention from the obvious initial lesion to the extension into the parametrium, we are faced with the double problem of preventing overtreatment to the paracervical triangle and, at the same time, of building up the dose that is delivered toward the lateral pelvic wall around point B. Here we must avoid oversimplification of our problem by realizing that point B is only a landmark, "sufficiently near the obturator node to give a reasonable idea of the dose there." Other lymph nodes along the lateral pelvic wall are equally important, extending all the way from the obturator foramen anteriorly to the hypogastric and ureterosacral nodes

posteriorly. Fletcher,[8] describes them as being arranged in a rectangular cuboid, lying against the lateral pelvic wall. The anteroposterior length of this area is about 10 cm., the depth from 5 to 7 cm., while the base is at least 50 sq. cm.

It becomes obvious that if internal radiation is to deliver an effective dose to this vital lymph node area without overirradiating the paracervical triangle, it is necessary, first, to place some of the radium sources as far lateral in the vaginal fornix as the anatomy of the patient will allow, and second, to maintain the lateral spread throughout the treatment time. If we can realize these objectives and can accurately determine the relationship between the radium sources and points A and B, we can estimate the dose to these points as a simple routine procedure. By establishing such a system of "dosage specification" in gamma roentgens, based not only on the amount of radium and the time, but also on the number of the radium sources and their actual position, we can avoid the inaccuracies of the term "milligram hours." The 2 cases illustrated in Figures 1 and 2 both received 9,000 mg. hr. of irradiation. In the former, the pelvic anatomy permitted a full 6 cm. between the outside capsules of the vaginal applicator with a dose to point A of 9,500 and to point B of 3,200 gamma roentgens, while in the second case a contracted vaginal vault restricted the spread to 4 cm. with a dose of 8,040 gamma roentgens to point A and only 2,370 gamma roentgens to point B. This is offered as an explanation of the difference in results in cases apparently receiving the same dose (in milligram hours), a variation usually dismissed as being due to difference in tumor cell resistance.

Specifications for an Applicator. Our aim was to develop a radium applicator that would overcome the difficulties we have experienced in maintaining the position of colpostats, bombs, and the bulk, weight and inflexibility of the expanding metal applicators. We wanted to use multiple sources of radiation as in the latter, these to be of low intensity, used for a correspondingly long time. The applicator must be easy to insert and must be adaptable to the wide variation of pathologic anatomy usually found in such cases. There must be a positive lateral spread of the radium sources which can be maintained during the long treatment time. The instrument should be of light weight and be tolerated in relative comfort by the patient. It must deliver a maximum dose to point B, without overirradiating point A. It is essential that a minimal dose be delivered to the bladder and rectum and that local "hot spots" be avoided. It must be loaded and handled with safety to personnel as well as to the patient.

FIG. 2. Anteroposterior roentgenogram of a case in which the regional anatomy limited the spread of the vault applicator to 4 cm.

The instrument that resulted from these specifications has been used in more than 80 cases. While it is too early to reckon results in terms of cure rate, our primary observations have been gratifying. There have been no instances of severe local reaction to the bladder, the ureters, rectum or intestines, in spite of the fact that we are giving a much higher milligram hour dose than we

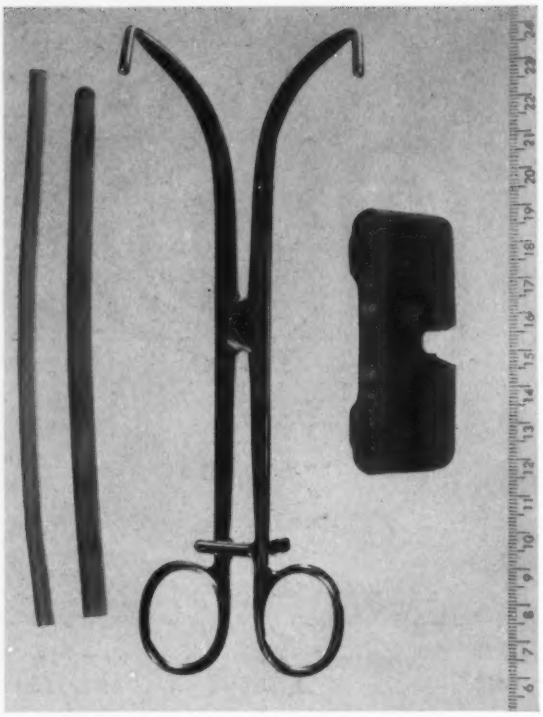

FIG. 3. Component parts of applicator. Left to right: plugging rubber, soft rubber intrauterine tube, the spreader handle and the vaginal vault applicator.

had been able to use with previous methods.

Description of the Applicator (Fig. 3, 4, 5 and 6). The instrument is in three parts —the uterine stem, the applicator for the vaginal vault, and the spreader handle. The uterine stem is a conventional soft rubber tube, No. 22 French, closed at one end, in which three capsules are placed in tandem in the usual manner, for insertion into the cervico-uterine canal.

The vaginal applicator, which is made of vulcanized gum rubber, measures 7 cm. in length, 3 cm. in its vertical dimension, and is 1 cm. thick. Along the top edge are the openings of eight cylindrical cavities for radium capsules, four evenly spaced on each of a 12 mm. center zone. The cavities, the centers of which are 7 mm. apart, are 4 mm. in diameter and 27 mm. in length. These dimensions were selected so that the majority of radium capsules in use could be accommodated. If short capsules are used, the vertical measurement of the applicator can be decreased for greater ease of insertion by trimming off an appropriate amount from the upper edge, using wet shears. The thickness of the walls of the cavities at the ends and on the front surface is 3 mm.

Toward the back surface, near the ends, are two sets of openings that extend from the upper to the lower edge. These are for attaching the spreader handle. The two outer openings are used when the vaginal vault is 5 cm. or more in width. When the vault capacity is less, one or both of the outer two cavities are removed by cutting vertically through the applicator at the median margin of the end cavities, using wet shears. The spreader prongs are then inserted into the center pair of holes. This reduces the over-all length of the applicator from 7 cm. to 5.5 cm., the capacity from eight to six capsules with a full spread between the centers of the end capsules of 4.5 cm.

The spreader handle is made of forged stainless steel. The intravaginal arms are curved so that they are of minimum width in both the open and closed position. At the ends of the arms are prongs, at a 135

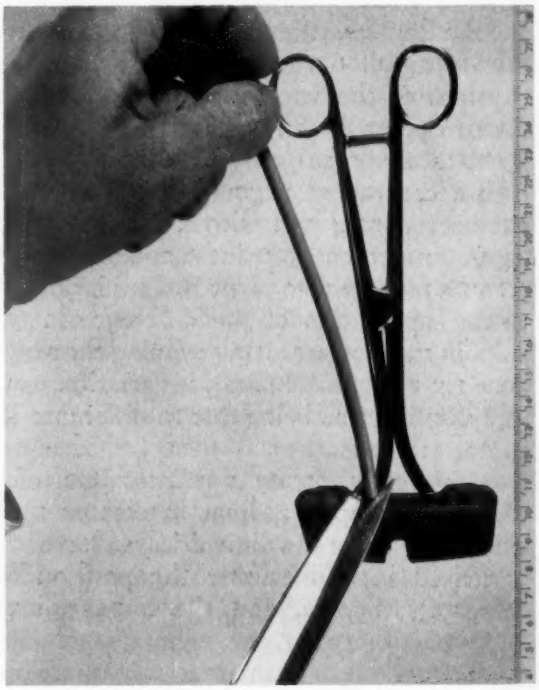

FIG. 4. Loading the applicator.

degree angle to the long axis of the arms, which slip into the prong receptacles of the applicator. The action of the spreader is of the "reverse scissors" type. When the handles are separated the prongs are brought together and the applicator folds into a small mass, comparable to that of a standard rubber bomb (Fig. 5), so that it can be inserted with ease in a vast majority of cases. When the handles are closed (Fig. 6) the arms separate. The handle is narrow enough to fit comfortably between the legs of the patient and can be inspected at intervals during the treatment in any questionable or difficult case to see that the position of the applicator has not changed.

Method of Loading (Fig. 4). The applicator can be loaded easily and quickly with a minimum of exposure to the operator. The fundamental principles of safe handling of radioactive material with long forceps from behind ar adequate lead barrier are to be observed strictly. First, the rubber applicator is attached to the spreader which now serves as a handle during the loading operation. Exposure is diminished if, after each capsule is placed in its receptacle, that hole is plugged by inserting the end of the length of plugging rubber until it contacts the end of the capsule. The plug is cut off with wet shears, leaving a small amount of the plug projecting above the surface of the applicator so that it can be grasped with forceps and removed when unloading the capsules for cleaning and storing after the treatment is finished. The applicator can be used an indefinite number of times.

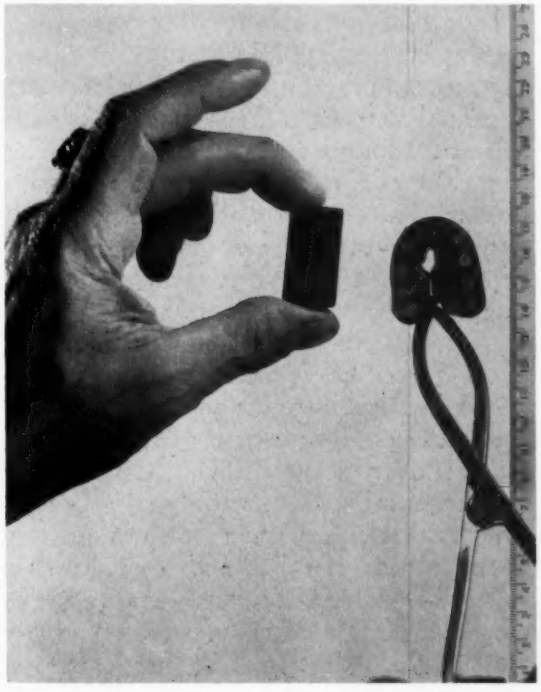

Fig. 5. Applicator in position for insertion. A conventional rubber London bomb is illustrated to show relative size.

Fig. 6. Applicator in the spread position with the intrauterine tube in position.

Sterilization. The loaded uterine stem and the vaginal applicator, with the spreader

handle still attached, are sterilized by immersion in any effective sterilizing solution that is not harmful to gum rubber and stainless steel. Alcohol, 95 per cent, or zephiran in 1 to 2,000 solution for at least one-half hour, is satisfactory. Methods of sterilizing with heat are to be avoided because of the danger of damaging the radium cells.

Inserting the Applicator. After dilatation of the cervical canal, the tandem stem is inserted into the canal until the end of the proximal capsule is just beyond the external os. The folded applicator is then introduced, using the spreader as a handle. It is then spread partly open and the portion of the intrauterine stem that projects into the vagina is guided through the notched opening in the lower edge of the applicator with forceps. When the applicator has been maneuvered up against the cervix, it is expanded into the fornices as far as the anatomy will permit and locked. Vaginal packing is used routinely to insure contact of the applicator against the cervix and the vaginal vault as well as to displace the bladder and rectum as far from the radium sources as possible. The perineal end of a T binder can be looped over the end of the handle to reinforce the upward pressure of the applicator.

One of the important advantages of this applicator, in common with several others,[1,5,9,24] is its positive spread and a minimum of danger of a shift of position of the radium sources during the treatment. By checking with roentgenograms, many observers have proved that migration of loose capsules and colpostats is the rule. Loose capsules, in spite of skillful packing, almost invariably shift toward the dependent posterior part of the vagina, close to or in direct contact with the rectum. Spring colpostats present similar problems. Howes[12] found that constant pressure of the colpostat against the wall of the vagina overcomes the normal tonicity of the vagina and allows the colpostat to expand during the treatment. Our experience has been that the spring tension decreases with repeated use. The spring is frequently overflexed during insertion so that its spreading function is destroyed. Medial rather than lateral displacement was the rule. The damage from overirradiation to the rectum and paracervical triangle that results from this unintentional concentration of radium sources in the midline, and the false impression of radium dose that results from the assumption that the radium has remained in place makes such systems of radium application unreliable.

Discussion of Radium Distribution. The use of multiple sources of radiation in an applicator has the advantages of multiple port cross fire technique in roentgen therapy. There are obvious advantages to be realized by placing eight radium sources, evenly spaced, over the entire vaginal vault, as compared with concentrating the same amount of radium into a few bombs. An intensive dose to a few points in the vault is prevented by spreading the intensity over a broad surface area, and the necessity of increasing distance by the use of thick bulky applicators is avoided.

Low intensity sources with a corresponding increase in treatment time is advantageous. Quimby[10] states, "It has long been known that when a given amount of radiation is administered rapidly to a living organism the effect is, in general, more marked than when it is administered slowly either by protracting or fractionating the exposure." In one of their experiments, where high intensity doses of gamma radiation were delivered in about five hours, a more marked effect on the tissues was produced in each instance as compared with equal doses of low intensity which were extended over several days. Our clinical experience is in accord with that of Corscaden and his co-workers,[2,3] who found that the incidence of injuries to the intestines was reduced from 8.9 per cent to zero by changing their method of administering a 7,000 mg. hr. dose from 175 mg. for forty hours to 70 mg. for 100 hours.

When we were considering the strength of the radium sources to be used, we were

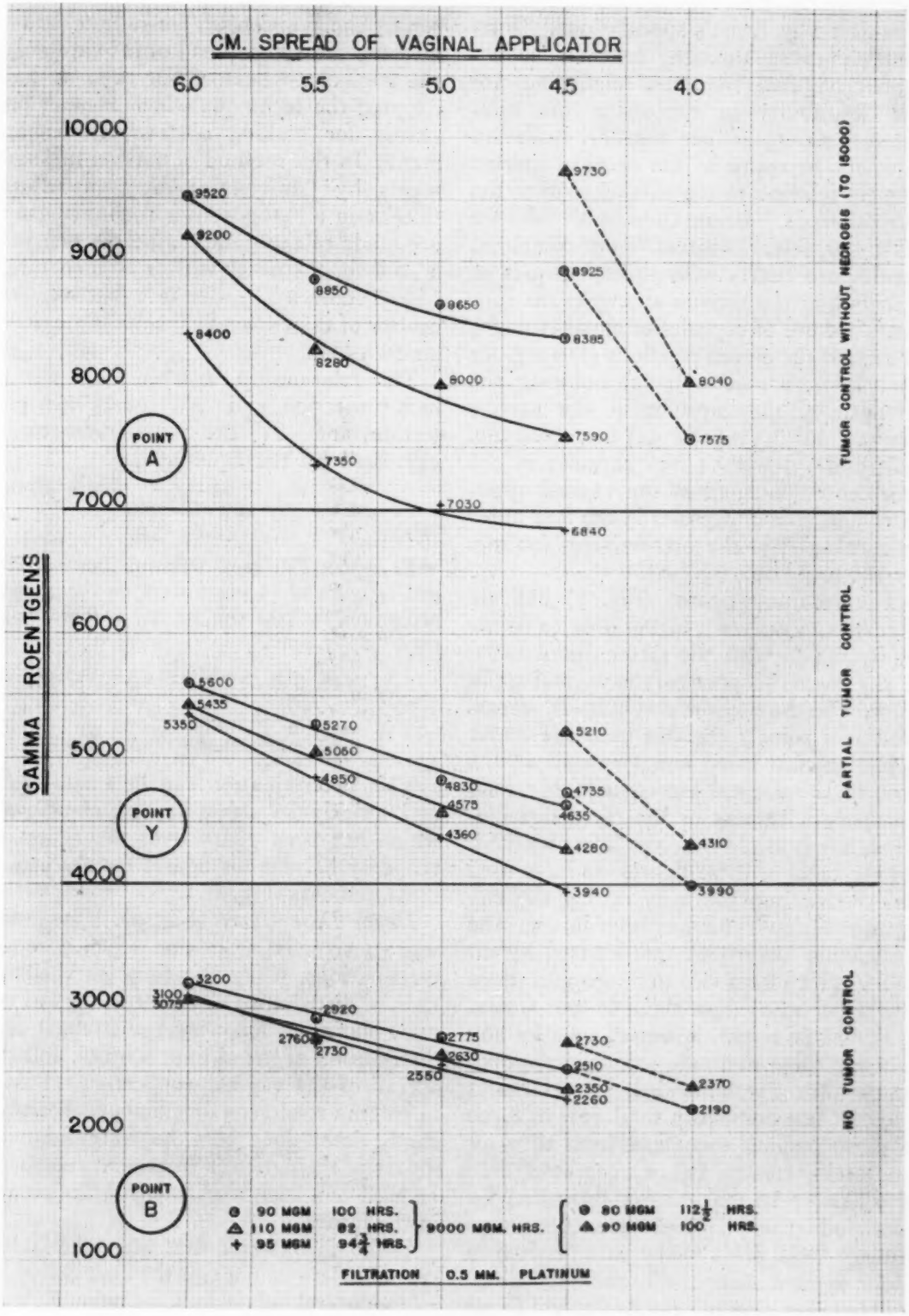

Fig. 7. Chart showing gamma roentgens delivered to points A, B, and Y, depending on the lateral spread of the applicator.

stimulated by Ernst's speculations:[5] "Further clinical evaluation, contrary to accepted physical concepts, might indicate the desirability of decreasing the total gamma roentgens per mg. hr. radiation intensity exposure in the cervical uterine stem in relation to the total dosage of the vaginal fields." Using Quimby's[22] "dosage table for linear sources," we computed depth dose charts with three methods of distributing the radium strength: the conventional use of capsules of equal strength in each of the eleven positions (110 mg. for 82 hr., 9,020 mg. hr.); (2) reducing the strength of the capsules in the uterine stem to half (95 mg. for 94¾ hr., 9,000 mg. hr.), and (3) with 5 mg. capsules in the four center positions of the vaginal applicator and 10 mg. capsules in the four outer positions and in the uterine stem (90 mg. for 100 hr., 9,000 mg. hr.).

The resulting figures (Fig. 7) indicate that we can deliver a higher dose to points A, B, and Y with the latter distribution, at any degree of spread of the vaginal applicator. The dose to the cervix itself, measured at a point 1 cm. out from the center of the cervical canal and 1 cm. above the level of the vaginal fornix, is higher than necessary with any of the three distributions, but is lower with the latter method. On the basis of these figures we have used this distribution routinely during the two years this applicator has been in use. The treatments have been fractionated by dividing it into from two to four applications over a period of from three to four weeks. It should be noted, however, that by any of these three methods the dose approximates that recommended by Margaret Tod[25,26,27] for point A, a total dose of 8,500 to 9,000 gamma roentgens from three or four weekly treatments, or a combined dose of 9,500 to 10,500 gamma roentgens by combined radium and roentgen rays through small fields to the parametrium in a four to six week over-all time.

Method of Determining Individual Depth Doses. Following insertion of the radium, roentgenograms (Fig. 1 and 2) are made to record the position of the radium and to measure the exact spread of the capsules in the vaginal applicator. For this, we have adopted the technique which Isaacs[13] presented for making obstetrical measurements. In this method of making measurements by "differential divergent distortion" two anteroposterior roentgenograms are made of the patient's pelvis, one with a 40 inch, the other with a 25 inch target film distance. The distance between the centers of the two end capsules is measured on each film.

The relationship between "*a*," the 40 inch projection, and "*A*," the 25 inch projection, and "*T*," the actual diameter, is expressed by the equation:

$$T = \frac{3Aa}{8A - 5a}.$$

Example: The measurements between the end capsules of Figure 6 were on the 40 inch projection, "*a*," 6.8 cm., on the 25 inch projection, "*A*," 7.4 cm.

$$T = \frac{3 \times 7.4 \times 6.8}{(8 \times 7.4) - (5 \times 6.8)} = \frac{150.96}{25.2}$$

$= 6.0$ cm., the actual spread.

This determination can be made easily and quickly by using Isaacs' nomogram, which has been adapted to the necessary range by halving his figures for obstetrical measurements (Fig. 8).

Depth Dose Chart (Fig. 7). The graph was constructed from our depth dose determinations, using the three methods of radium distribution. The filtration was 0.5 mm. platinum. Knowing the strength and distribution of the radium sources, and the spread of the vaginal applicator, the dose in gamma roentgens for points A, B and Y can be determined from the chart and made a part of the patient's treatment record, to be used as a basis for comparison of results in the future.

It should be noted that when the lateral spread is less than 4 cm. the dose delivered to the lateral pelvic wall, at point B, is so small as to be of relatively little value. When such unavoidable limitations are

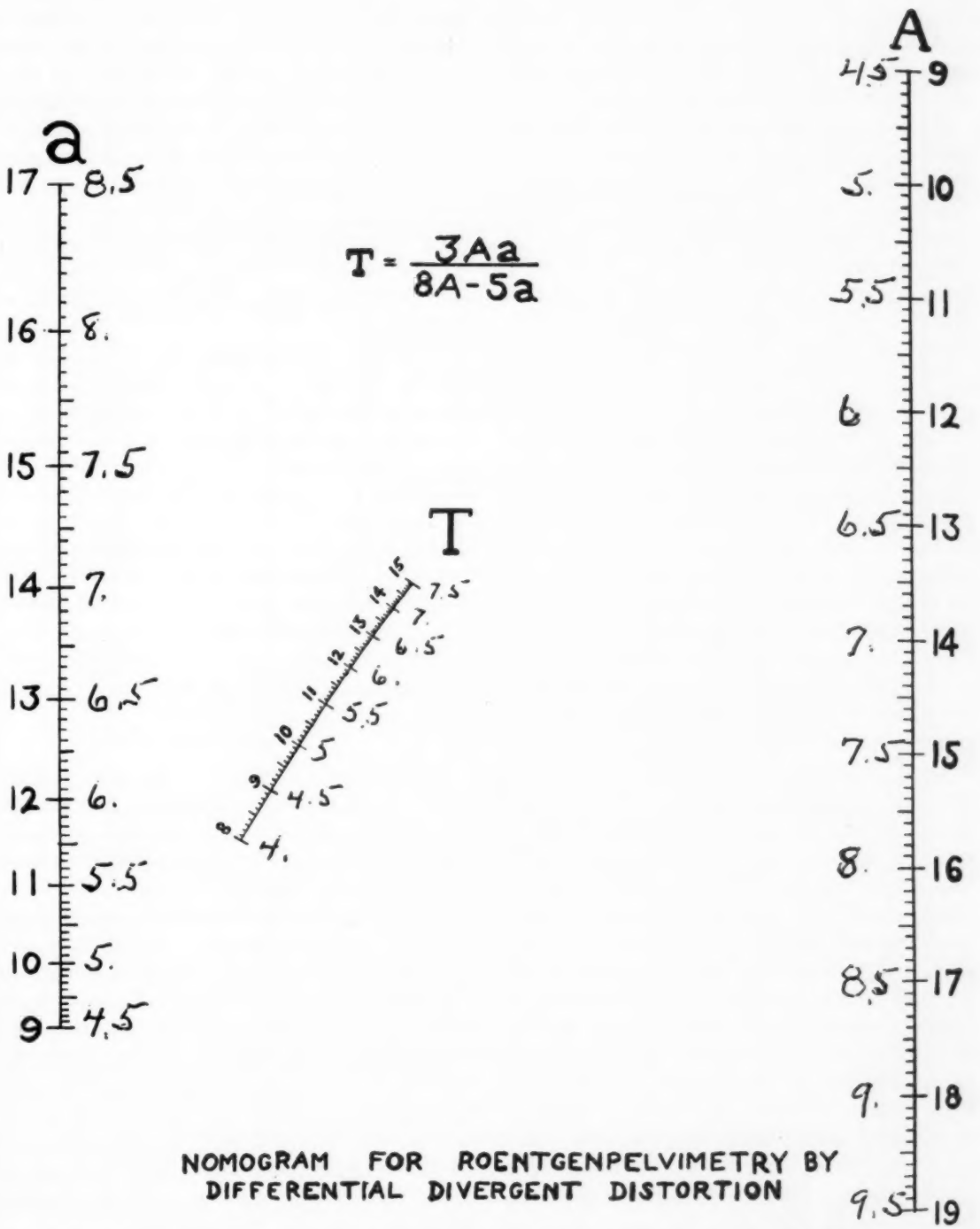

Fig. 8. Isaacs' nomogram. The lower value figures are used in determining the actual width of the spread of the capsules in the vault applicator. (Republished, with numerical modifications, by permission from Isaacs.[13])

present the value of internal radiation is more or less confined to the cervix and the paracervical triangles, and roentgen therapy must be depended upon for practically the entire dose lateral to point Y.

The graph also demonstrates that the dose to the paracervical triangle, point A, can always be kept above 7,000 gamma roentgens, that is, within the "zone of tumor control without necrosis;" that the dose to the mid-parametrium, point Y, is always in the "zone of partial tumor control;" while the dose at the lateral pelvic wall, point B, is always in the "zone of no tumor control."

Roentgen Therapy. It is not within the scope of this paper to discuss roentgen therapy per se, yet its role in supplementing the inadequate radium dose to the parametrium and the pelvic lymph nodes deserves a few comments in an effort to promote a more skillful combination of these two inseparable modes of irradiation, neither of which is adequate by itself in the treatment of cancer of the cervix.

With the high gamma roentgen dose that is delivered to the cervix, uterus and the paracervical triangles, it is unnecessary and even undesirable to add further radiation to these midline structures. While additional roentgens cannot be entirely eliminated because of backscatter, they can be kept to a minimum. With narrow ports, the beam should be directed perpendicularly, avoiding any tendency to cross fire toward the midline. A zone 4 to 5 cm. wide in the midline anteriorly should be left untreated. These right and left fields can be treated simultaneously by using a divided cone, as recommended by Richards,[23] or a divided field can be effected by fitting a strip of heavy lead, 4 cm. wide, through the center of a 15 by 15 cm. cone. Posteriorly, a single midline port over the sacrum adds effectively to the dose to the presacral lymph nodes. The lateral lymph nodes are reached through two sacrosciatic or gluteal ports and with two narrow lateral perineal ports through the obturator foramens, as recommended by Fletcher *et al.*[9]

The role of surgery in relation to radiation therapy is not yet clearly defined, even in large medical centers. As recently as 1947, Meigs[16] said, "It should be distinctly understood and emphasized that the operation [Wertheim] is not an attempt to compete with irradiation in cancer of the cervix. Irradiation is the present treatment of choice and it has not been proved that the surgical procedure is as good or better. Surgery distinctly should not be made the goal of all operating surgeons for all but a very few cases are much better handled by irradiation." Due to technical difficulties of radical surgery of the Wertheim type, it seems safe to predict that in most communities radiation therapy must continue to be the chief weapon. To be worthy of the challenge the irradiation techniques must be improved. We urge more "intelligent exploitation" and zeal in the use of intracavitary radium to match that of del Regato[4] when he said, "Your results in the treatment of carcinoma of the cervix can only be improved by your intelligent exploitation of external roentgen radiation."

CONCLUSIONS

A radium applicator for use in the treatment of cancer of the uterine cervix is presented, together with a system of estimating and recording the depth dose, which, it is hoped, will help correct the inaccuracies of recording dosage so common with intracavitary radium therapy.

Made of soft rubber, the distinguishing features of the applicator are that it is flexible, easy to insert, conforms to the contours of the vault, and can be expanded and held to the widest spread permitted by the regional anatomy of the patient.

The applicator and the instrument to introduce it, spread it and hold it in place are of light weight and are tolerated without discomfort by the patient.

Local reactions, in spite of high dosage, are kept to a minimum by the use of multiple radium sources of low intensity and by both protracting and fractionating the exposure.

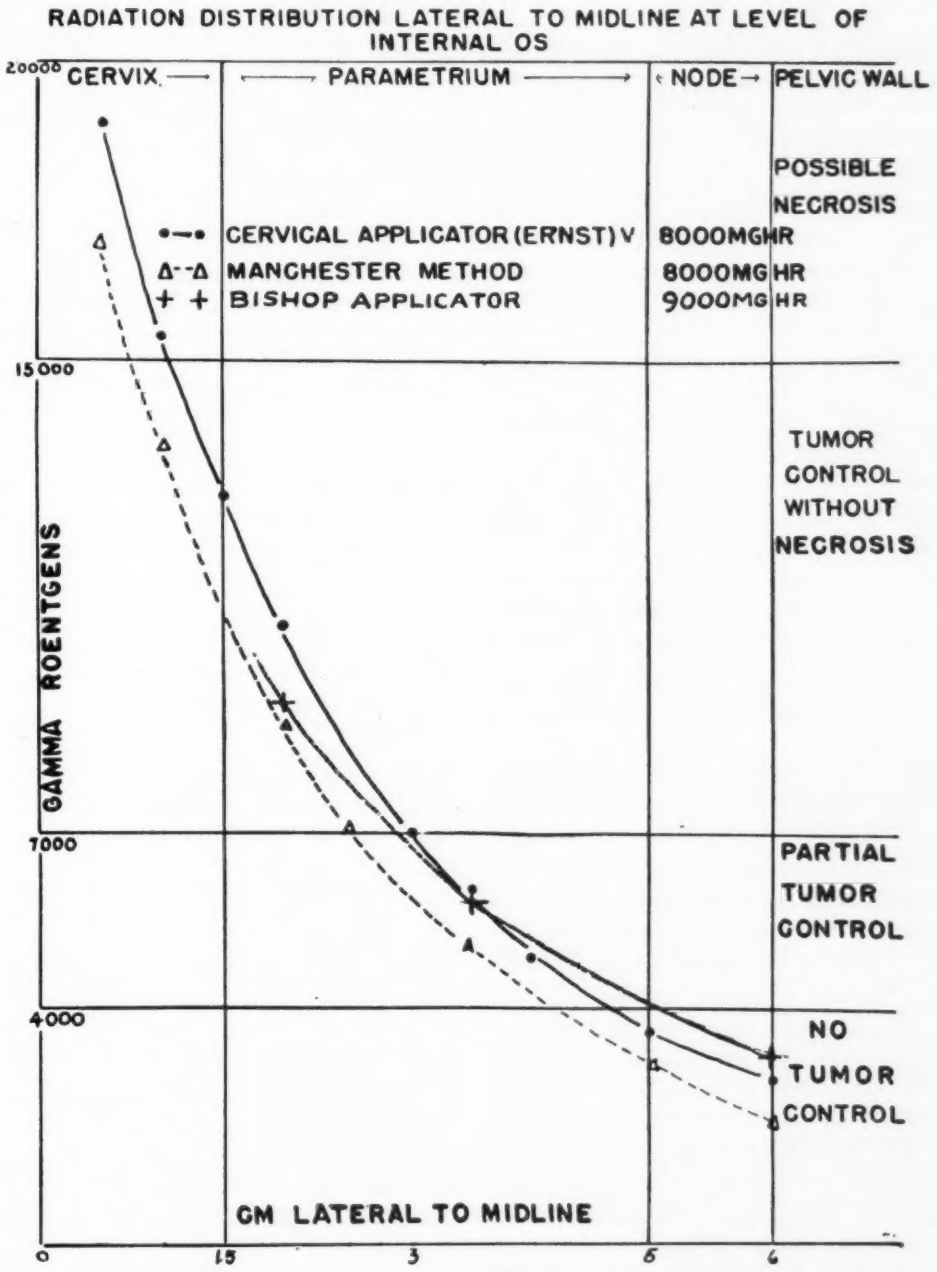

Fig. 9. Ernst's chart,[6] comparing the dosage delivered by his applicator and by the Manchester system to which has been added the dosage by our applicator.

It can be loaded and handled with safety. The depth dose is comparable with other accepted methods (Fig. 9).

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We wish to express our indebtedness to Dr. Robert A. Kimbrough, Director of the Division of Obstetrics and Gynecology of the Pennsylvania Hospital, and his entire staff for their encouragement and cooperation, to Miss Selena Black, R.N., Chief Radiological Technician, for her invaluable technical help, and to Mr. Paul Schuster, of The Budd Company and Mr. Walter Butterworth, for constructing the spreader handles.

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NEUTRON CAPTURE THERAPY WITH BORON IN THE TREATMENT OF GLIOBLASTOMA MULTIFORME*†

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IN 1940 Kruger[6] reported some *in vitro* experiments of thermal neutron capture by boron-10 (B^{10}) on the survival of transplants of mouse sarcoma, mammary carcinoma and lymphoma, and concluded that the results indicated that "neoplastic cells can be destroyed *in vivo* if sufficient boron in some suitable form can be applied to the tumor *in vivo*." Later the same year Zahl, Cooper and Dunning[15] reported on effects on transplantable mouse sarcomas injected with boron or lithium preparations and exposed to a thermal neutron source. They concluded that a significant increase in tumor regression followed the exposure and could be attributed to localized ionization resulting from the nuclear disintegration products of the capture process. In 1941 Zahl and Cooper[16,17] reported studies on the localization in tumors of lithium and certain lithium salts of dyestuffs as possible neutron capture agents for tumor therapy. They published data showing that lithium compounds injected intravenously into mice concentrated to a degree in spontaneous mammary tumors and implanted tumors of the sarcoma strain and that the concentration of elemental lithium within the tumor mass some four hours after injection was sufficiently great to provide a significant source of radiation through thermal neutron capture. Neither Li^6 nor adequate neutrons were available at this time to permit extension of this work. They also computed the possible effectiveness of B^{10} as compared to Li^6 and discussed to some degree the possible advantages of thermal neutrons over roentgen rays and fast neutrons for tumor therapy. With a selective localization factor of only 2 times for the tumor over other tissues in the mouse and a concentration of 0.03 per cent lithium in the tumor, they estimated a gain of 43 per cent in radiation dosage to the tumor over the other tissues. In 1948 Tobias, Weymouth, Wasserman and Stapleton[14] reported studies on biological effects induced in animals by thermal neutron radiation following administration of uranium. They, however, reported no studies of uranium distribution in tumors.

Also during 1940 there appeared a preliminary report by Stone, Lawrence and Aebersold[10] on the use of fast neutrons in the treatment of malignant disease. Subsequently in 1942 a fuller report on fast neutron therapy was made by Stone and Larkin[11] and a follow-up report by Stone[12] on late effects was published in 1948. It was Stone's conclusion that the results with fast neutron therapy were not encouraging because of the severity of the late reactions. It must be emphasized that the present study deals with thermal or slow neutrons, the fast neutrons having been screened out, and that the effects are mediated by providing a target substance, B^{10}, which becomes an alpha radiation source by virtue of slow neutron capture. The direct effects of slow neutrons on tissue are not depended upon for results in the present study, as was done with fast neutrons in the earlier work.

In 1951, with the completion of Brookhaven's large nuclear reactor designed for

* This research was done under the sponsorship of the Atomic Energy Commission.

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experimental studies, thermal or slow neutrons became available in sufficient quantity to permit certain biological investigations. The development of procedures to achieve neutron capture therapy was among the first projects of the Medical Department. While engaged in studies of the kinetics of distribution of solutes through body water and a search for a suitable carrier for a capture element, we learned of the significant work of Sweet and associates[5,13] since published on boron distribution in brain tumors and normal brain of patients. The work herein reported is a collaborative effort beginning in 1951 of the group at Brookhaven and the group at the Massachusetts General Hospital to apply in a practical manner the advantages of neutron capture to therapy of glioblastoma multiforme. These studies, involving a very considerable effort by a large number of people, could not have been done without the generous assistance of members of the Reactor Science and Engineering, the Health Physics and Instrumentation, and the Chemistry Departments of Brookhaven, and members of the technical and nursing staffs of the Medical Department at Brookhaven. It is a pleasure to acknowledge the vital assistance received from these groups.

During the past two years 10 patients with proved glioblastoma who had been operated upon at the Massachusetts General Hospital were transferred to the Brookhaven National Laboratory for neutron capture therapy. Glioblastoma has to date proved refractory to treatment surgically or by means of conventional radiation therapy and therefore a new approach to control is justified in this surely fatal disease. On each patient studies were done at operation on boron distribution between tumor and normal brain. The patients were then observed for a preirradiation period at Brookhaven, followed by neutron capture therapy at appropriate intervals.

A limited number of elements have the capacity to capture thermal neutrons with subsequent disintegration by emission of an alpha particle. B^{10} is one of the most favorable to select because it has a large thermal neutron capture cross section of 3,990 barns.[8]

Commercial boron is composed 81 per cent of B^{11} and 19 per cent of B^{10}. The B^{11} has a cross section of 4.5 millibarns and a neutron capture results in a neutron-gamma reaction which is unsuited to our purposes. This makes imperative the use of B^{10} as the only suitable boron isotope for thermal neutron capture therapy of the type we have envisaged. We obtained from the Atomic Energy Commission Laboratory at Oak Ridge an enriched preparation containing about 96 per cent B^{10} and only 4 percent of B^{11}. From this enriched mixture of metallic boron, borax was synthesized at first in the Chemistry Department at Brookhaven by Dr. H. A. Finston[3] and later in the Medical Department.

The alpha particles resulting from the B^{10} reaction ($B^{10}+n^1 \rightarrow Li^7+\alpha^4$) have an energy permitting penetration of tissue to a depth of only 9 microns.[1] Therefore if the boron distribution be limited to the tumor area highly selective local radiation of great biological effectiveness can result. This, if sufficient in intensity, may result in annihilation of the tumor structures while leaving surrounding normal tissue intact because of the very limited penetration of the alpha particle radiation.

The physiological assumptions made by us in this therapy are few and simple. When a soluble substance is injected intravenously it will distribute in a characteristic manner throughout the body water. Its distribution may be limited to extracellular fluid or it may distribute between intracellular and extracellular fluid in a distinctive way. The concentration of the material in any given tissue water at any given time will be determined by qualities of that tissue and of the injected substance. In the central nervous system most substances pass through the capillary walls slowly, exhibiting an effect of what has been termed the blood-brain barrier. In glioblastoma there occurs within the tumor

a destruction or disappearance of the blood-brain barrier, thereby permitting certain solutes to distribute through the tumor mass at a more rapid rate than through normal brain. Eventually equilibrium will obtain but during the pre-equilibrium period there will exist for a variable but short interval of time a significantly greater concentration of such an agent in tumor water than in normal brain tissue water (Fig. 1). Exposure of this volume to neutrons during this pre-equilibrium period permits neutron capture to proceed in the tumor with resulting radiation to its structure, while surrounding normal tissue is unaffected because of the low concentration of capture element. Thus a precise knowledge of the time-concentration relationship existing among components of what may be designated as a three-compartment system may make possible selective radiation of a given type of tissue beyond its radiation tolerance. These bases are discussed more fully elsewhere.[2]

Calculations which have been made at Brookhaven and data which have been obtained by Sweet at the Massachusetts General Hospital suggest that in the case of boron administered intravenously a maximum concentration is reached in tumor tissue about ten to fifteen minutes after injection.[13] It is estimated that thereafter for a period of at least forty-five minutes the concentration differences between tumor and normal brain are such as to permit effective neutron radiation for capture therapy.

A facility for medical neutron radiation has been provided in the reactor at Brookhaven. By removing a part of the shielding over the top of the reactor it was possible to provide a radiation port of presumably sufficient flux without undue exposure of the whole body. The general details of this facility are shown in Figure 2.

Effective irradiation of the tumor is dependent upon the neutron flux, the concentration of capture element and the time of exposure. Rather extensive studies reported in detail elsewhere[9] have been done with phantoms made of tissue equivalent plastic and tissue equivalent liquid, together with observations of activation of gold wires placed externally on the patient's head and inserted within the head at various levels about the tumor. From these data it has been possible to construct a first approximation of isodose curves. A summary of this is shown in Figure 3.

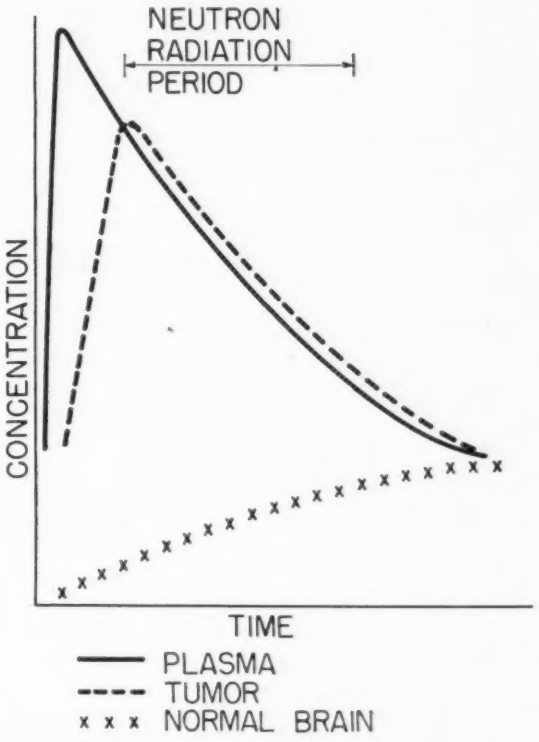

Fig. 1. Relationship with time between plasma concentration, tumor concentration and normal brain concentration of boron following intravenous injection of boron. The maximum tumor concentration is shown at approximately twelve minutes post-injection and a neutron irradiation period of forty minutes is indicated.

Immediately prior to irradiation the borax solution was injected intravenously in a volume of 100 milliliters. The dose of borax averaged 20 grams, which provided from 19 to 46 milligrams of boron per kilogram of body weight. Injection time averaged about seventy-five seconds and, immediately upon completion of the injection, the patient's head was fixed in the proper position over the radiation port with cotton web straps weighted by lead

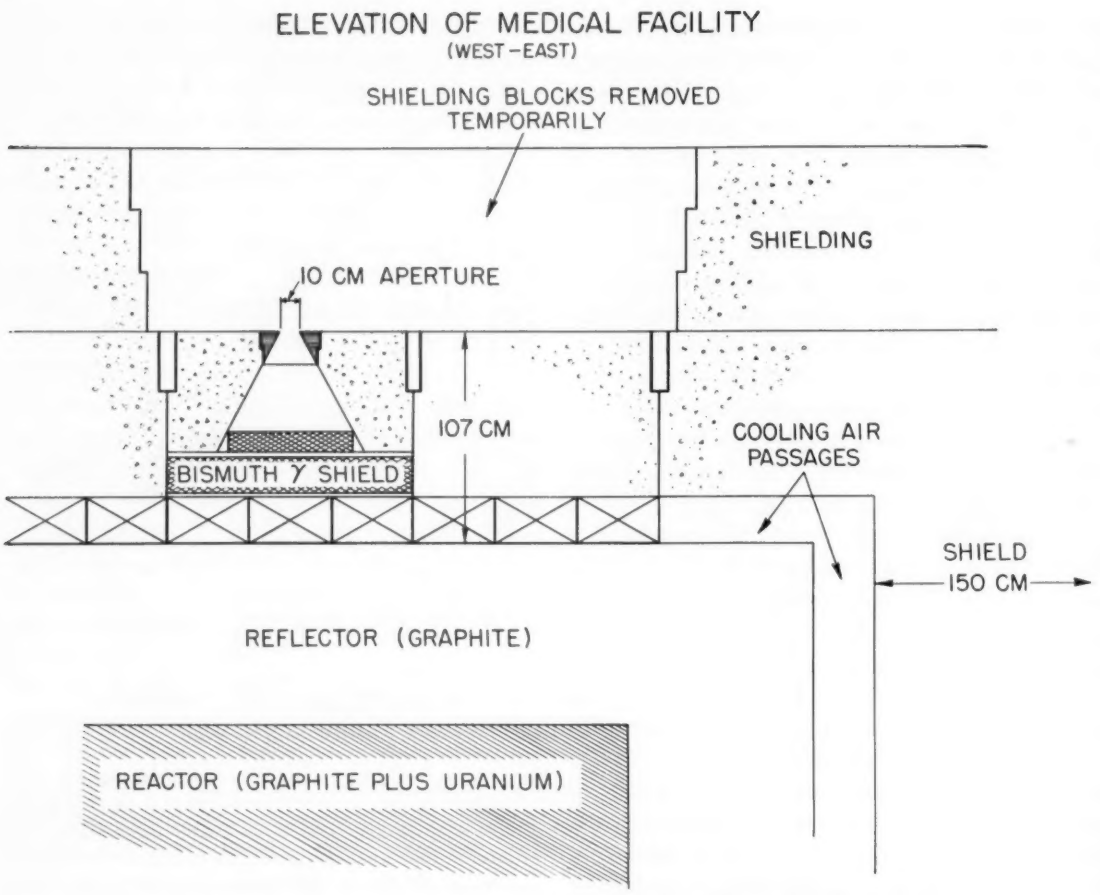

Fig. 2. Schematic diagram of facility at the reactor showing relations of shielding to source of radiation.

bricks. The reactor was then brought to full power as rapidly as could be done with safety. About eight to ten minutes were required for this operation. Our estimations of the occurrence of maximum concentration of boron in the tumor were also ten to twelve minutes postinjection. Approximately a thirty to forty minute period of neutron radiation was then given, with the major exception of the first patient who received only seventeen minutes of irradiation.

The treatment of the patients is divided into two series—the first, comprising 5 patients receiving only a single neutron irradiation followed by a period of observation to determine if any untoward effects developed, and the second, comprising again 5 patients who received from two to four irradiations.

Since our hypotheses for conditions of treatment are predicated upon an intact blood-brain barrier, it became necessary to make observations upon the effect of neutron radiation upon this barrier. Observations made first upon dogs showed no demonstrable effect on the barrier by up to ninety minutes of neutron radiation. Subsequently we observed the effects on 3 patients through multiple irradiations measuring the blood-ventricular fluid barrier as a standard. The rate of appearance of radioactive sodium, chloride, bromide and phosphorus and the nonappearance of inulin and sucrose in ventricular fluid were observed. No significant changes occurred,

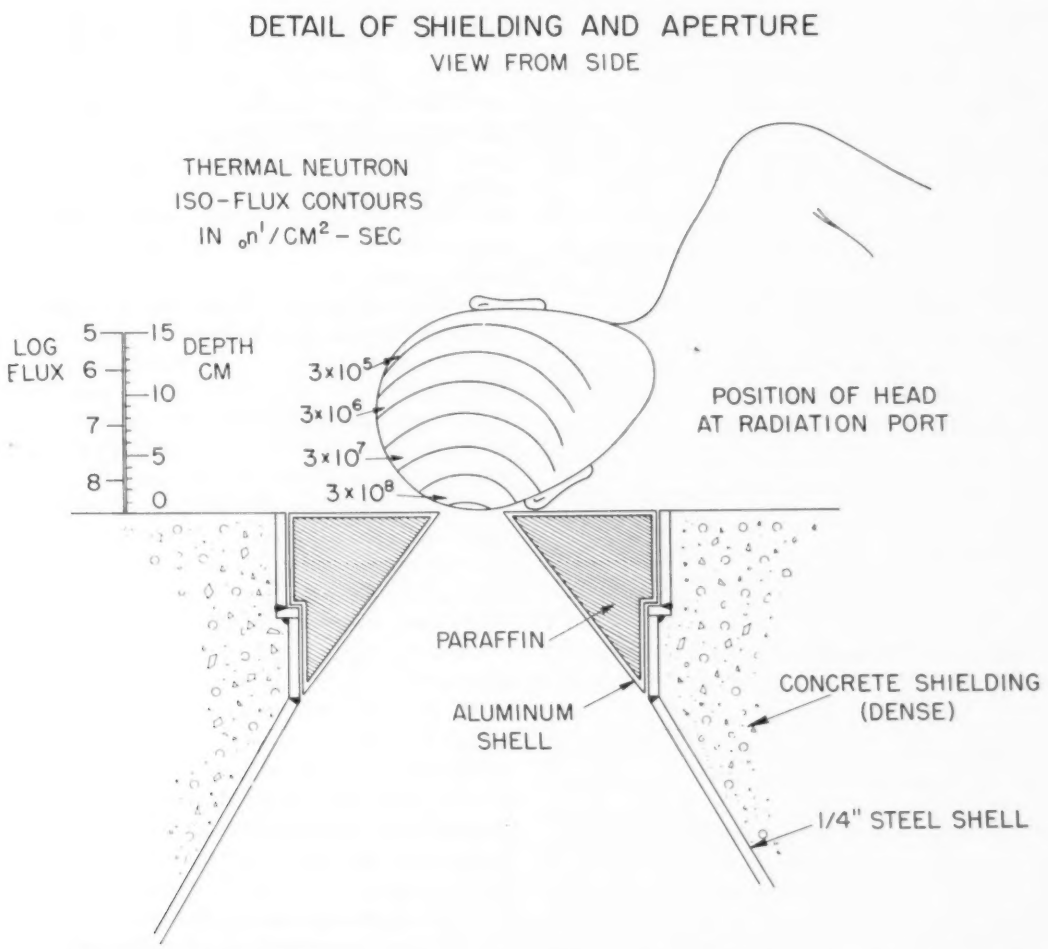

Fig. 3. Neutron isodose curves imposed on outline of human head showing approximate attenuation with depth. Details of irradiation port are also shown. The port has a length of 10 cm. in this sketch; its other dimension is 5 cm.

from which we have tentatively concluded that within the limits of exposure thus far explored with the present available neutron flux, no effects result on the blood-brain barrier. These studies are being reported in detail elsewhere.[7]

RESULTS

In the series of patients thus far treated by this method no conclusive results have been obtained and all 10 patients are now dead. However, rather uniform clinical responses were observed in our patients and all of these suggest that tumor growth was at least retarded to some degree by the procedure. Complete pathological studies on sections obtained in 8 patients have not yet been finished and these will be reported in detail elsewhere.[4]

In the first group of 5 patients, each receiving a single neutron treatment, the results will be discussed chronologically in the order of their treatment.

Patient No. 3977 (P. J.) was a fifty-one year old woman upon whom craniotomy three months previously had revealed an inoperable glioblastoma involving the temporal lobe. Prior to neutron capture therapy the patient's course appeared to be slowly progressive, most marked in deterioration of speech understanding, so

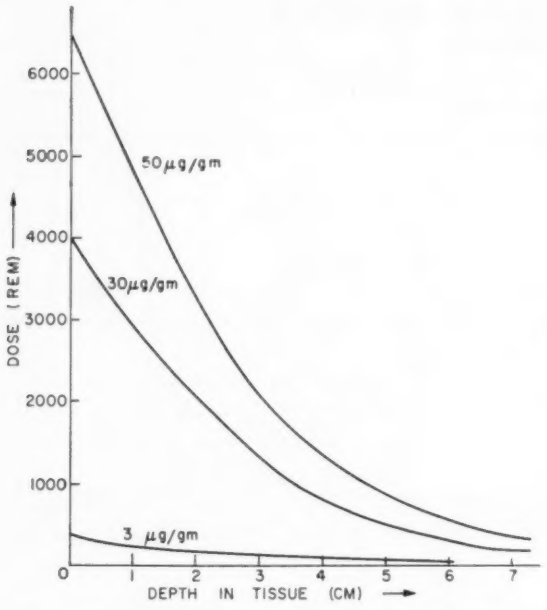

Fig. 4. Depth dose of radiation delivered by the B^{10} n alpha reaction assuming an incident skin flux of 3×10^{8} n/cm^2/sec., a radiation exposure of forty minutes and a relative biological efficiency of alpha particles of 20. The radiation dose for each of three concentrations of B^{10} is shown.

that for four weeks prior to therapy she was unable to communicate except for indication of body needs to the nursing and medical attendants. On February 15, 1951, after intravenous injection of 1.59 grams of B^{10} as borax, she was irradiated for seventeen minutes during which period a total of 0.44×10^{12} neutrons per square centimeter reached the presenting skin surface. Within several days after treatment she could speak effectively, relate incidents which had occurred prior to treatment, and could respond to requests effectively. Motor incapacities in the right arm changed little but the patient desired to be and was ambulatory contrasted with previous unwillingness to get out of bed. Approximately six weeks post-treatment, progressive and definite deterioration set in; the patient became bedridden; the capacity for speech was lost and motor function of the right arm disappeared. Sixty-three days after irradiation, papilledema was noted and the patient suffered a series of jacksonian seizures. On the sixty-fifth day after irradiation she became comatose and died on the sixty-seventh day with signs of increased intracranial pressure. This was approximately fourteen months after beginning of initial symptoms and five months after the diagnosis had been made.

Patient No. 4055 (W.L.), a thirty-eight year old man, developed first symptoms one month prior to surgical exploration which revealed an aggressive glioblastoma involving the left temporal lobe. Only 75 per cent of the tumor was excisable. For thirty-seven days postoperatively the patient had shown rather rapid deterioration with signs of increased intracranial pressure despite decompression, and one week before irradiation survival for more than a few days appeared very doubtful. Immediately prior to irradiation, insertion of beta probe counters used to localize the lesion resulted in total aphasia. A dose of 1.7 grams of B^{10} as borax was given intravenously and the patient was irradiated for thirty minutes and received a total neutron dose of 1.42×10^{12} neutrons per cm.^{2} at the skin surface. For the first twenty-four hours following irradiation an increase in pre-existing right-sided weakness and in the size of the decompression was noted. Thereafter there was progressive improvement so that within several days he was able to stand unaided, could speak a few words, understood clearly commands given and showed a return in size of the decompression to pre-treatment levels as evidenced by cephalic circumference. For the next three weeks there was no increase in head circumference, after which increase in size of the decompression was noted and deterioration in performance developed. Because of increasing intracranial pressure, he was returned to the Massachusetts General Hospital for re-exploration, which was done. No further improvement resulted from removal of a large mass of tumor sixty days after irradiation, and the patient died ninety-three days after irradiation.

Patient No. 4045 (G.F.), a sixty year old man, was operated upon one month prior to admission and extensive resection of the right parietotemporal and occipital lobes was carried out with residual tumor existing. Prior to irradiation, and following operation, the patient improved generally for one month but without specific neurological betterment. During the two weeks before irradiation he developed severe headaches and showed increased cerebrospinal fluid pressure. He was treated on March 22, 1951, receiving 1.47 grams of B^{10} borax intravenously followed by irradiation for thirty minutes, receiving 1.46×10^{12} neutrons per cm.^{2}

at the skin. Treatment was uneventful. No change in the gradual deterioration was noted following irradiation and the patient developed clinical signs of tumor in the left hemisphere. Increased cerebrospinal fluid pressure became more prominent and death occurred forty-three days following irradiation. Gross autopsy findings showed extensive tumor extension to the left side.

Patient No. 4202 (J.M.), a fifty-four year old man, was operated upon 125 days prior to irradiation and one month following onset of symptoms. A very extensive excision of the right temporal, parietal and occipital lobes was carried out. Postoperative recovery was uneventful and, except for a hemianopsia and minimal impairment of the left extremities, the patient was admitted to Brookhaven in good condition. On June 14, 1951, he was given 1.69 grams of B^{10} as borax intravenously, irradiated with neutrons for thirty minutes for a skin dose of 1.42×10^{12} neutron per cm.^{2} The procedure was well tolerated but on the fourth postirradiation day the onset of lethargy was noted which progressively increased rapidly. Lumbar puncture yielded bloody fluid at increased pressure and withdrawal of fluid resulted in relief of symptoms. Within twelve hours a second tap was required and thereafter repeated taps were necessary to control the increased cerebrospinal fluid pressure. Blood gradually disappeared from the fluid but the patient slowly became progressively worse and died 126 days postirradiation.

Patient No. 4227 (A.R.), a forty-seven year old man, was operated upon 152 days prior to admission and one month after onset of symptoms. A large cystic tumor involving the parietal and occipital lobes was removed but P^{32} studies at the time of operation indicated remaining tumor in the thalamic area. On admission to Brookhaven National Laboratory Hospital the day before irradiation the patient showed only left-sided impairment of sensation and an incomplete left-sided hemianopsia. Speech, reading, thought and memory were unimpaired and he had successfully been carrying on his profession of college teaching. Following pneumoencephalography, 1.69 grams of B^{10} borax given intravenously, he received thirty minutes' irradiation for a total skin neutron dose of 1.42×10^{12} neutrons per cm.^{2} He had exceedingly severe headache persisting for six days. Ten days after irradiation he appeared unchanged from admission. No elevation of cerebrospinal fluid pressure was found before treatment. Immediately following discharge the patient left on a trip to South America. On August 15, 1951, two months postirradiation, he suffered recurrence of headaches and underwent a retrogressive course to death 100 days after radiation treatment.

To recapitulate the results in the first 5 patients, each of whom was given a single neutron irradiation: In one patient, No. 3977 (P.J.), there had occurred a striking clinical improvement to the observers at the bedside which was maintained for approximately six weeks. In a second patient, No. 4055 (W.L.), there was a temporary cessation in enlargement of the decompression area lasting about three weeks. In the third patient, No. 4045 (G.F.), in whom no improvement was recorded, the unsuspected tumor growth contralaterally, in an area where attenuation of the neutron flux precluded any possibility of therapeutic effect, provided an excellent control on immediate effects and susceptibility of the observers to suggestion. In patients four, No. 4202 (J.M.), and five, No. 4227 (A.R.), no assessment of treatment was possible. It was obvious at this time that more than one thermal neutron irradiation would be required.

The second group of 5 patients each received multiple neutron irradiations.

Patient No. 4653 (A.B.), a fifty-eight year old man, suffered an attack with loss of consciousness for a few minutes, twenty-four days prior to craniotomy at the Massachusetts General Hospital on October 26, 1951. No symptoms preceded this first attack. At operation a resection of the frontal lobe extended medially to the falx and included all but the precentral, inferior frontal and posterior part of the orbital gyri. Postoperative recovery was good and he was admitted to Brookhaven National Laboratory Hospital on December 11, 1951. At this time speech and intellectual facilities were not impaired. Weakness was present in the left arm and leg and the patient complained of pain in the left upper arm. On December 13, 1951, he was given 2.02 grams of

B^{10} as borax followed by thermal neutron irradiation for a neutron skin dose of 1.47×10^{12} neutrons per cm.^{2} No pneumoencephalography was done. Following irradiation the patient was alert, had less arm pain and walked about during the day. Three days after exposure a mild dermatitis over the area exposed to the irradiation was noted. He was discharged home December 18, 1951, in good condition.

He was readmitted January 7, 1952, and during the intervening three and a half weeks had grown much weaker, was not able to walk without assistance from two people and had suffered increasingly severe pain localized in the left upper arm. On admission there was now marked weakness on the left side and the patient was not oriented as to time or place. Speech was markedly slurred. Patient had great difficulty in concentration. On January 8, 1952, he was given 2.12 grams of B^{10} as borax intravenously and received a neutron skin dose of 1.93×10^{12} neutrons per cm.^{2} A pneumoencephalogram was not done prior to treatment. Following therapy the patient became alert and briskly cooperative. By January 16 he was walking without assistance and with only a slight shuffle in his gait. He was discharged home on January 25 with evidences of definite skin reaction over the neutron exposure area over which epilation of second growth hair was now seen.

He was readmitted March 10 and it was evident that the postirradiation improvement in sensorium and muscle strength on the left had been maintained during the interim. Pain in the left arm had grown more severe and the patient still had seizures, but infrequently. He had continued throughout on dilantin therapy. On March 11, without antecedent pneumoencephalography, he was given 2.12 grams of B^{10} as borax intravenously followed by his third neutron irradiation for a neutron skin dose of 0.93×10^{12} neutrons per cm.^{2} On discharge he was alert, cheerful, witty and enjoying life. The severe pain in the left arm had disappeared by the third postirradiation day so that demerol previously given, 50 mg. t.i.d., to control the arm pain, was discontinued and no analgesic therapy was required. The patient was discharged March 18 and for at least four to five weeks remained as above while journeying about Florida.

He was readmitted on April 24, 1952. At this time the patient was retarded in thought and speech. Neurological examination showed no change from the previous admission except for continued absence of pain in the left arm and the recent occurrence of episodes of hypesthesia of the left heel. On April 25 the patient was given his fourth neutron capture therapy, again without antecedent pneumoencephalography. For this treatment he received 1.69 grams of B^{10} as borax intravenously and a neutron skin dose of 0.98×10^{12} neutrons per cm.^{2} The patient was lethargic after treatment and became somnolent with generalized weakness developing over the following ten days. Psychic depression was marked. A rise in temperature to 39° C. on the fifth postirradiation day was seen without ascertainable cause. On discharge May 9 the patient showed considerable generalized weakness, lethargy, hypesthesia and hypalgesia on the left, a definite left lower facial weakness and a distinct retardation of thought and speech. During the next month the course was retrogressive and the patient died on June 15, 1952. An autopsy was done.

Patient No. 4737 (T.F.), a fifty-nine year old man, was first operated upon June 20, 1949, when a temporo-parieto-occipital lobectomy for glioblastoma multiforme was done at the Massachusetts General Hospital. Symptoms of severe headaches began about April 25, 1949. Following operation, which was presumed to be total extirpation of the neoplasm, the patient was able to carry on his work and felt well. He had a left homonymous hemianopsia, an absent left ankle jerk and a positive left Babinski. The patient did well until September, 1951, when headaches recurred. He was operated upon November 14 and a cystic cavity containing 50–60 ml. of fluid was aspirated. This occupied the volume of the previous resection. In the posterior inferior part of the right temporal lobe remnant frank neoplasm was removed. On January 10, 1952, further removal of cystic wall and tumor was carried out.

The patient was admitted to Brookhaven National Laboratory Hospital on February 8, 1952. At this time he had an unsteady gait, was rather confused; his memory was poor and some neurological changes were noted on the left side. He received 2.12 grams of B^{10} as borax intravenously on February 12, 1952, and was irradiated for thirty minutes with thermal neutrons for a skin dose of 0.86×10^{12} neutrons per cm.^{2} No encephalography was done. He was discharged home February 19 essentially unchanged from admission neurological examination.

He returned to the hospital on May 9, 1952. During the intervening period he had appeared improved to his family, being more self-reliant and responsive for seven weeks, and then in the subsequent three weeks had failed rapidly to the point where he was no longer able to walk, to sit up without support or to use his left arm or hand effectively due to sensory deficits. He had become somnolent and devoid of initiative. Significant admission findings were poor articulation of speech, almost complete sensory loss on the left side and generalized weakness. Coordination was particularly weak on the left and was also imperfect on the right. On May 2 he was given 2.12 grams of B^{10} as borax intravenously and irradiated with thermal neutrons for a neutron skin dose of 0.70×10^{12} neutrons per cm.^{2} He improved rapidly after treatment and on discharge seven days later was able to stand alone, walk with assistance, feed himself, and made effective use of his left hand in manipulating matches, cigarettes and newspapers. At home he continued to improve as above until the end of the month when over a two day period he became weak and ataxic with headaches and was unable to sit up even in bed. Nausea became prominent and he was hospitalized in Concord, New Hampshire, on June 2. A large dose of demerol was given and after sleeping twenty-four hours the patient awoke refreshed, alert and with no headache. Subsequently, speech, movement and coordination improved but periods of mental confusion persisted. The patient then gradually deteriorated to death on June 27, 1952. Autopsy was obtained.

Patient No. 4709 (P.P.), a fifty-four year old man, developed memory loss and mental confusion at the end of December, 1951. He was operated upon January 11, 1952, and a left anterior temporal lobectomy with subtotal removal of glioblastoma multiforme was carried out. Recovery from operative procedures was satisfactory and on January 22, 1952, he was admitted to Brookhaven National Laboratory Hospital. His general condition was poor. During the next two months there was little change in the patient's condition. He was semicomatose most of the period but for short intervals on occasion could comprehend requests and demands. A right hemiparesis was present. Increased intracranial pressure required frequent taps. On February 14 and 25 radioactive argon (A^{41}) was injected into the tumor area after removal of fluid. There was no change noted in his slowly progressive course. Preneutron therapy examination on April 8 showed a stuporous, hemiparetic man with normal vital signs and good vegetative functions. On this date 2.12 grams of B^{10} as borax were injected followed by thirty minutes of neutron irradiation for a neutron skin dose of 0.93×10^{12} neutrons per cm.^{2} During the first two weeks following this treatment the patient appeared to lose his usual lethargy and to be alert and agitated. He made jaw movements suggestive of talking. Increased intracranial pressure again demanded frequent taps to prevent excessive pressures. This did not appear to be exaggerated nor decreased following treatment.

On April 22 he was given his second neutron treatment. For this he received 2.12 grams of B^{10} as borax intravenously and a neutron skin dose of 0.70×10^{12} neutrons per cm.^{2} The third post-treatment day the patient appeared very toxic with elevation of the white blood cell count, decreasing hemoglobin and marked increase in intracranial pressure with low blood pressure. Transfusions, ventricular taps and supportive therapy carried him over a difficult three week period. On May 12, because of further deterioration, ventricular taps were discontinued and the patient went into deep coma. Following the second irradiation an infection of the area of dermatitis over the exposure field had developed and was treated locally. Healing, though slow, was steady. Despite clear evidences of extension of the tumor contralaterally it was decided to treat the patient a third time with neutrons and this was done on June 20. Before treatment the patient showed shallow, rapid respirations, gray color, and several times during the day required stimulants. Borax injection of 2.12 grams of B^{10} and treatment that evening were, however, well tolerated, and following treatment he appeared in unexpectedly good condition with satisfactory vital signs. The neutron skin dose for this treatment was 0.72×10^{12} neutrons per cm.^{2} However, the patient declined steadily and on July 11 was noted to be deeply jaundiced. A diagnosis of serum hepatitis was made. The patient's condition grew rapidly worse and death occurred July 14, 1952. An autopsy was obtained.

Patient No. 5227 (J.H.), a fifty year old woman, in April, 1952, noted that she was failing and seemed tired and apathetic. In August, 1952, she had a seizure, again in September,

and several in the next few weeks. She was admitted to Baker Memorial Hospital, Boston, on October 2, 1952. The patient was diabetic and also had rheumatoid arthritis. On October 4, 1952, a partial left frontal lobectomy was carried out to remove a glioma. The tumor was over 6 cm. in diameter. Postoperative recovery was satisfactory and she was discharged on October 20.

She was admitted to Brookhaven National Laboratory Hospital for the first time on November 4, 1952. Her general condition seemed good except for a severe mixed aphasia, slight right hemiparesis, moderately severe diabetes and chronic rheumatoid arthritis. Her first boron-neutron treatment on November 7 was well tolerated. She received 2.12 grams of B^{10} as borax intravenously and a neutron skin dose of 0.91×10^{12} neutrons per cm.^{2} It was noted on the seventh postirradiation day that her general condition was about the same as on admission except for the impression that she was brighter and mentally more alert. There was a slight residual edema about the left side of the head associated with erythema and pigmentation. She was discharged on November 19 with no clear change in her neurological status. On December 1 she was readmitted. During the intervening three weeks she had developed increased weakness on the right and frequent urinary incontinence. She appeared more alert than on the previous admission, was cheerful and communicative and although her aphasia was severe her vocabulary seemed to have increased and she was speaking in more coherent phrases. On December 5 she was given her second treatment despite belief that her neurological condition was rapidly deteriorating. For this treatment she received 2.12 grams of B^{10} as borax intravenously and a neutron skin dose of 0.82×10^{12} neutrons per cm.^{2} On the sixth postirradiation day it was noted that she was somnolent most of the time. On January 7, 1953, thirty days after treatment, she was in precarious condition. This was believed due to thalamic invasion by the tumor and atelectasis at the base of the left lung. After slight improvement in general condition following hemotherapy on January 9 she was given her third neutron irradiation. For this she was given 2.02 grams of B^{10} as borax intravenously and received a neutron skin dose of 0.80×10^{12} neutrons per cm.^{2} The treatment lasted thirty-five minutes and was well tolerated. Subsequently hemotherapy, digitalization and oxygen were required but without avail and the patient died on January 12. Autopsy was obtained.

Patient No. 5144 (A.H.), a thirty-three year old woman, developed diplopia, severe headaches and left-sided weakness in April, 1952. On May 12 a right parietal craniotomy was done with removal of a large cerebral glioblastoma multiforme. On June 27 a second craniotomy was done to remove all additional identifiable neoplastic tissue. Following this second extensive resection the patient made a postoperative recovery and was admitted for the first time to Brookhaven National Laboratory Hospital on September 10, 1952. The patient had no specific complaints and was cooperative although almost totally helpless with a left hemiplegia, a left homonymous hemianopsia and an indwelling catheter because of bladder hypertonia and poor control. Her recent memory showed gross impairment. The large decompression area was soft.

On September 12 she was given 2.12 grams of B^{10} as borax intravenously and irradiated for forty minutes. Neutron skin dose was 0.96×10^{12} neutrons per cm.^{2} By discharge on October 8 she was alert (for her) and well oriented. This had developed within the first two days after treatment. She could partially feed herself and could smoke a cigarette by herself. The left lower extremity could be adducted and the fingers of the left hand extended. Epilation began fourteen days after irradiation and a definite dermatitis, dry and scaly, was seen at the time of discharge.

She was readmitted on November 5. Her condition was essentially unchanged except for increase in weakness on the left side, less vision and increased sensory loss. On November 7 she was given her second neutron capture therapy; 2.12 grams of B^{10} as borax were given intravenously and a neutron skin dose of 0.91×10^{12} neutrons per cm.^{2} By November 10 erythema of the exposed area was marked and later this area broke down, became infected and healed slowly. Assessment on December 11 showed improvement. Tests were performed better than before, an equivocal Babinski had disappeared, right abdominal reflexes had returned, there was less facial weakness and reflexes on the right side were more normal. The patient continued to be more alert. On January 9, 1953, she was again treated with 2.12 grams of B^{10} as borax

given intravenously and a neutron skin dose of 0.96×10^{12} neutrons per cm.^{2} Little change was noted in the patient following this treatment. On February 6 she received her fourth neutron radiation after a similar B^{10} injection. The neutron skin dose on this occasion was 0.90×10^{12} neutrons per cm.^{2} The treatment was well tolerated but no change in the patient's condition could be firmly detected. On the afternoon of February 11 the patient suddenly became stuporous with elevation of blood pressure to 170/90 but no elevation of intracranial pressure. She remained semi-stuporous, failed to respond to drugs and died that evening. Autopsy was obtained.

Considering as a group the 5 patients who received multiple neutron capture treatments, it is our belief as observers of these patients at the bedside that in 3, No. 4653 (A.B.), No. 4737 (T.F.), and No. 5144 (A.H.), there was temporary evidence of improvement following one or more of the irradiations. In patient No. 4709 (P.P.), the results were equivocal but possible betterment may have occurred following treatments one and three, while in patient No. 5227 (J.H.) we observed no improvement following any of the three exposures. The best results were seen in No. 4653 (A.B.) who received the largest total neutron dose and at the highest rate. Statistically there was no evidence of significant prolongation of life in these patients, though particularly in No. 4653 (A.B.), who had a tumor with histopathological evidence of rapid growth at the time of operation, and with initially an apparently rapid retrogressive course, events during the period of treatment suggested a real prolongation of life in this individual. We are aware of the difficulties of immediate prognosis in these patients and for purposes of therapeutic evaluation have endeavored to require some definitely objective sign of improvement, such as relief of pain sufficient to permit discontinuation of analgesic drugs such as occurred in No. 4653 (A.B.), or marked improvement in muscular coordination without specific training such as occurred in No. 4737 (T.F.). The absence of conclusive results in this series of patients may well be explained by a consideration of probable dosage which is discussed in more detail later.

As yet we have not been able to determine with any degree of accuracy the dosage which was delivered to the tumor. Strenuous attempts were made to construct an alpha sensitive probe counter but satisfactory instruments were not developed. Nor do we have accurate analyses of blood during the runs since the patient could not be approached during the neutron exposure. Analyses of tumor tissues taken serially immediately after boron injections are available only for doses of 0.5 gram of B^{10} given as borax[13] and not in the amounts used during therapeutic trials. Since the neutron dose diminishes significantly with distance from the port, the effectiveness of irradiation is greatly dependent upon position.

Despite all these uncertainties presently existing, some parameters of dosage can be estimated. Relations between boron concentration, neutron flux and dose are shown in Figure 4. The radiation dose resulting from thermal neutron capture by the B^{10} has been calculated by us in REM (roentgen equivalent man). The REM as used herein is obtained by multiplying the energy absorbed in the tissue by the RBE (relative biological effectiveness) which is taken as 20 for the alpha radiation. If one assumes the tumor tissue to lie at a depth from 3 to 7 cm. from the surface of the head, an incident flux of 3×10^8 n/cm^2/sec. will have decreased to 10^8 at a depth of 3 cm. and will be approximately 10^7 at a depth of 7 cm. The radiation dose resulting from thermal neutron capture by the B^{10} at these fluxes will therefore vary from 1.2 REM per minute per microgram B^{10} per gram of tissue at 3 cm. depth to 0.12 REM per minute per microgram B^{10} per gram of tissue at a 7 cm. depth. For each thirty minute treatment period there will then be delivered 36 REM per microgram of B^{10} per gram of tissue. The boron dose in our patients ranged from 20 to 46 micrograms per gram body weight and assuming an average tumor concentra-

tion of boron of these values during the treatment, a reasonable conservative assumption, the dosage delivered to the tumor structures from boron alone would amount to from 720 to 1,756 REM at a depth of 3 cm. with the flux available. At a 7 cm. depth the dose will decrease to one-tenth of this value. We believe from clinical considerations alone that the dose delivered to the tumor area in these patients was a minimal therapeutic dose and this is in agreement with the above considerations. The maximum probable radiation from B^{10} to normal structures would be one-third of that delivered to the tumor, and in some patients with a better than 3:1 tumor-brain distribution the normal tissue dose will be significantly less. Sweet and his collaborators have observed ratios of 12:1 and 24:1 to exist in these patients. It is apparent that both concentration and flux are critical in attaining satisfactory dosage and we are vigorously studying systems which will give us more information regarding the behavior of boron under these conditions.

The complications of therapy thus far have been few and of relatively minor significance. One group of effects was due to boron and a second to irradiation. The injections of borax were followed uniformly by vigorous retching for a few minutes and not infrequently evacuation of bowels and bladder. A short period of respiratory arrest was noted in 1 patient about one hour after injection and poor color of the patient was seen following the majority of injections. In 2 patients a papular skin rash was noted followed by desquamation in about five to ten days. No untoward effects on renal function were observed.

Following irradiation, erythema of the skin outlining the irradiation port was seen in the majority of runs. A single neutron exposure resulted in temporary epilation, while two or more exposures resulted in permanent epilation over an area somewhat larger than the exposure port. Pigmentation of the skin lying over the irradiation port was uniformly observed. Fragile, parchment epidermis has been seen in 3 patients after their second neutron exposures and, although this area is very susceptible to pyodermic infection after minor trauma, healing was uneventful but slow. Only topical treatment was used. Further irradiation did not aggravate the condition. Two patients who also received multiple irradiation did not show this type of skin response. None of the patients showed it after a single neutron exposure. In 2 patients capable of cooperation, slit lamp examinations of the lens were done and no changes suggestive of cataract formation were observed. Examination was carried out as much as 140 days following the first neutron exposure in 1 patient who received four irradiations. Ordinary ophthalmological examination showed no changes in any of the patients. The longest period of observation was 186 days following the first irradiation. In no patient were significant decreases seen in the number of circulating lymphocytes in the peripheral blood.

SUMMARY

(1) The feasibility has been shown of the use of a nuclear reactor to provide a neutron source for boron-10 capture therapy of glioblastoma multiforme.

(2) A series of ten patients were treated of whom five received a single irradiation; one patient received two irradiations; two patients each received three irradiations, and two patients each received four irradiations. Multiple irradiations were in general given at five to six week intervals.

(3) Temporary amelioration of clinical symptomatology suggestive of retardation of tumor growth was seen to occur following eight of twenty-one capture therapy efforts, questionable improvement in six of the remaining thirteen efforts, and no detectable change following seven of the treatments. Only one of five patients receiving multiple treatments registered no improvement at any time.

(4) Periods of observation of up to six months during which patients received up

to four capture therapy procedures have revealed no serious complications of this therapy.

(5) Further extensive exploration of neutron capture therapy is warranted.

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DISCUSSION

Paul C. Aebersold, Ph.D., Oak Ridge, Tennessee. I welcome the opportunity to discuss this very interesting paper by Dr. Farr and his associates. As one of the group at the Radiation Laboratory, Berkeley, California, who first investigated the biological effects of neutrons and later who attempted fast neutron therapy of patients, I had always hoped, and still do, that in some way neutrons may be used for therapy. Neutrons produce heavily ionizing particles either by collisions with nuclei or by nuclear reactions. They also have special absorption characteristics. Soon after the discovery of neutrons, just over twenty years ago, it was recognized that neutrons would have powerful biological effects and in unique ways. It is unfortunate that this powerful and unique radiation did not immediately lend itself to cancer therapy.

It is gratifying to see this new attempt being made to use neutrons for therapy. Several factors now make for greater possiibilities of success than in the various pre-war attempts.

The first two factors are physical: (1) Enriched isotopes may now be obtained, permitting more tumor dose for a given chemical toxicity; and (2) very intense, highly collimated beams of thermal neutrons are now available from nuclear reactors, thousands of times more intense than from the cyclotron.

The other factors are biological: (1) Treatment in these cases is attempted on the basis of a very short-term, non-equilibrium selectivity, lasting for matters of minutes, rather than on a longer term selective uptake requiring hours to days: and (2) the type of tumor selected, both because of location and capillary characteristics, permits suitable neutron beam penetration and selective localization.

It should be pointed out that using an en-

riched isotope does not increase the selectivity; the isotope will have the same increased enrichment in all tissues. Using five-fold enriched B^{10} does, however, mean that the amount of boron required in the tumor need be only one-fifth as much as with normal boron. The enriched isotopes Li^6 and U^{235} have also been investigated by some experimenters as potential materials for neutron capture therapy. Should any other isotope look feasible, we could no doubt now concentrate it by methods developed during World War II.

The penetration in tissue of a slow or thermal neutron beam is fairly limited. Using a beam with an energy spectrum extending from thermal to higher energies would permit greater penetration. I would like to ask Dr. Farr what are the *optimum* as well as the *limiting* depths of treatment with the present Brookhaven beam, and to what extent these might be increased.

As Dr. Farr pointed out the alpha particle in the B^{10} reaction penetrates only 8 microns of tissue. This is less than cellular dimensions and means that for the B^{10} to be effective it must either get inside the tumor cells, on the surfaces of the cells, or in the intercellular fluid immediately surrounding the cells. Although ionic movement into cells can be rapid, I wonder whether the B^{10} in these cases gets into the tumor cells themselves in sufficient concentration to produce the destruction internal to the cells or whether most of the effect is from external bombardment. I would like to ask whether studies have been made of the detailed cellular distribution of the B^{10}.

In this connection, since there are no radioisotopes of boron to use for tracer studies, I wonder whether a secondary type of radioautograph would be possible for studying B^{10} distribution. The tissue sections containing B^{10} could be mounted next to a photographic emulsion as for a radioautograph and then irradiated with thermal neutrons; the alpha particles ejected from the B^{10} into the emulsion should show the B^{10} distribution.

It should be noted that an alpha particle and a lithium nucleus are released in the B^{10} reaction. If it requires release of only one of these particles in a cell to kill it and if considerable B^{10} gets inside cells, then the effectiveness of many of the released particles is lost and the effective dosage should not be figured solely on the total energy released. If most of the killing is due to particles impinging on cells from the surface or outside, then all the particles may be useful in killing and the effective dosage should be calculated from the total energy released. In the calculations of "roentgens equivalent man" given in the tables I wonder whether any such factor related to number of particles was considered and also what factor of relative biological effectiveness was ascribed to the released particles.

It is hoped that the studies mentioned by the authors to provide more accurate information of total integrated dose given to the tumor will soon be completed. These are essential to an understanding of what is happening and will no doubt indicate improvements in technique.

Although all the physical and biological factors have not been worked out and it is too early to discuss clinical results, I believe with the authors that the possibilities for neutron capture therapy are so attractive that further extensive exploration is warranted.

In closing, as a side remark, I wish to say that although the role of reactor thermal neutrons directly for therapy is still to be determined, indirectly these neutrons play a great role. Thermal neutrons in nuclear reactors produce the copious amounts of radioisotopes now so widely used in therapy. As contrasted with immediate use of the neutron reaction in the case of B^{10}, the neutrons in the radioisotope case are stored in an unstable nucleus and do not cause effects until the radioactive disintegrations which take place later.

Dr. Lee E. Farr. Thank you, Dr. Aebersold, for those very kind remarks.

This is an exceedingly complicated problem. We realize that there are very many areas in which our knowledge is sadly lacking, and we hope in the future we may be able to fill in some of these areas. The essential of our concept is that a nonspecific target substance, such as boron, lithium or any other capture element can be used under these circumstances if we know its precise physiological behavior, for then we can be reasonably certain it will be present in the treatment area in requisite concentration at the time of neutron exposure.

In regard to the optimal radiation dose, the optimal dose is higher than what we have been able to give. We are limited in part by the maximum available thermal neutron flux of our reactor. One should probably have a thermal neutron exposure throughout the tumor aver-

aging, let us say, 10^9 neutron, which is higher than we can at present attain. However, by increasing the dose of boron which is given one can in part overcome this difficulty. We are giving 20 gram doses now. This is about 30 micrograms per gram of body weight. We have been able to give seven times this dose in mice, daily for five days, without untoward effects, and we now feel encouraged that we may be able to at least double the dose which may be given to the human.

If we can get a surely certain boron concentration of perhaps 50 micrograms per gram of tumor mass, then the treatment should be effective, even with the present flux.

I should like to ask two of my colleagues who are here to answer two other questions which you brought up, Dr. Aebersold.

Dr. James S. Robertson. Dr. Aebersold suggested the possibility of increasing the effectiveness of this treatment by including some fast neutrons in the beam and depending on the slowing which occurs in the tissue to provide a higher depth dose of thermal neutrons.

Our thinking along this line has been in the other direction; that we should try to keep out fast neutrons. Part of the reason has been the desire to avoid the skin damage from fast neutrons reported by Dr. Stone, Dr. Aebersold and others of the group in California,* although it is true some skin damage has occurred even with the present arrangement.

* Ref. 10, 11 and 12 in present paper by Farr *et al.*

The other factor to be considered is that the number of slow neutrons one can get from fast neutrons is rather small. The flux measures not the number of neutrons involved, but the number of times that they cross a certain barrier. Fast neutrons are counted much more often than slow ones, so you lose a great deal in terms of flux in thermalization.

We have thought that it would be much better to increase the initial dose of slow neutrons than to depend on any slowing down of fast neutrons for the depth dose. Perhaps the best depth dose effects would be attained by the use of epithermal neutrons, those with energies slightly above thermal.

Dr. E. E. Stickley. On the matter of relative biological effectiveness, the curve you have seen was based on a factor of 20, which may seem high, although it is accepted in the literature.

Two things help to justify the use of this factor. One is that we actually achieve a somewhat higher total neutron dose than the case which was reported as typical. Another is that a large part of the energy—or at least an appreciable part—is carried by a lithium recoil particle, which may have an even higher biological effectiveness, being heavier than the alpha particle, and thus giving a denser ionization.

Another question asked by Dr. Aebersold concerned the use of photographic methods to track the alpha particles. We are doing some of this in our depth dose work, but it is still in an early stage.

BLOOD RETENTION OF INTRAVENOUSLY INJECTED COLLOIDAL PRODIGIOSIN IN NORMAL AND ROENTGEN IRRADIATED RABBITS*

AN INDEX OF PHAGOCYTIC FUNCTION IN THE RETICULOENDOTHELIAL SYSTEM

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THE blood retention of intravenously injected colloidal prodigiosin has been shown in this laboratory to be an index of phagocytic function of the macrophage system in normal and roentgen irradiated rabbits.[23–27] Following whole body 250 kilovolt roentgen radiation exposures of 800 roentgens or more, significant alterations in dye retention occur, whereas lower doses (300 r) fail to induce such changes although it is known[12] that leukopenia occurs in rabbits following exposures in this 300 r dosage range. Because of these and other observations, it appears that the increased blood retention induced by larger doses (800–1,200 r) is related mainly to depressed phagocytic function of the reticuloendothelial cells. Therefore, tests for blood retention of colloidal prodigiosin may be found useful for both diagnostic and prognostic purposes in determining the degree of radiation injury and in predicting the onset of recovery in rabbits.

These studies were prompted by two sets of observations in rats and mice given $LD_{50/30}$ doses of whole body roentgen radiation exposures. The incongruity of finding, on microscopic examination, macrophages having normal appearance and containing phagocytized bacteria and debris, in conjunction with a high incidence of positive blood cultures, led to the belief that there must be a functional abnormality in the reticuloendothelial system.[23] A temporary depression of phagocytic and related functions in these cells could account for the bacteremia, at least in part. Before undertaking investigation of this hypothesis, a review of pertinent literature revealed considerable evidence tending to support it. Warren and Whipple[31] originally described the phenomenon of bacterial invasion of the blood stream as influenced by roentgen-ray destruction of the mucosal epithelium of the small intestine. Chrom[7] has shown that intravenously injected bacteria are cleared more slowly from the blood stream of roentgen irradiated mice than from normal controls. Bloom[3] has demonstrated microscopically that the neutrophiles in irradiated animals present little or no evidence of phagocytic activity. Furthermore, the phase of relative functional inactivity in the spleens of irradiated rabbits (800 r) occurs between the first to ninth days post-irradiation.[3] Warren and Gates[30] described the process of experimental radiation pneumonitis. Liebow, Warren and DeCoursey[17] have described the manifestations of bacterial complications along with the radiation-induced pathological changes in man from tissue specimens collected in Japan after the bombings at Hiroshima and Nagasaki. In addition, Tullis[29] has studied the tissues of swine following whole body exposure to 1,000 kv. roentgen rays and has found that there is evidence of lowered resistance to infection, ascribed to the associated anemia, anoxia and depression of lymphoid and myeloid cells. However, since the most primitive hemapoietic cells —the reticular cells—are relatively radioresistant, Tullis suggested that the effort to reduce mortality does not seem to be al-

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together hopeless and that management of total body radiation disease should be directed at prevention of secondary infections and treatment of anemia, impaired circulation and anoxia.[29]

Recently Howland and his associates[14] have investigated the possibility of reducing radiation mortality in various animals from bacterial complications by the administration of antibiotics and transfusions and have also determined not only the incidence of bacterial invasion, but also the antibiotic sensitivity of the flora in the bowel of animals before, during, and after antibiotic therapy. Although results were promising with initial trials, the rapid development of resistant organisms became a serious obstacle during these studies. The work of Miller and his associates[18,28] likewise demonstrated the importance of bacteremia in the radiation syndrome of mice and the initial effectiveness of certain antibiotics given separately or in combination. In view of this supporting evidence, we were encouraged to pursue the problem basically by attempting to prove whether whole body ionizing radiation injury did or did not cause temporary depression of phagocytic function in the macrophage system.

The main purpose of this report is to present data on the blood retention of colloidal prodigiosin, as influenced by whole body roentgen irradiation. Additional information is submitted to lend substantiation to the basic hypothesis that colloidal prodigiosin particles are initially removed from the blood by the cells of the reticuloendothelial system. This proof includes determination of the prodigiosin content in various body tissues following intravenous injection, observation of the effect of India ink blockade and chloroform-induced liver damage on prodigiosin and bromsulfalein blood retention, and evaluation of the effect of shielding the liver-spleen areas with lead during radiation exposure on liver and phagocytic function. Furthermore, the interrelationships between alterations of phagocytic function, spleen size, mortality and bacteremia are discussed with respect to the development of bacterial complications in the radiation syndrome. Pharmacological stimulation of phagocytic function in conjunction with other supportive measures is suggested as an adjunct in the management of the radiation syndrome.

EXPERIMENTAL

The procedures, equipment, reagents and methods of dye standardization and tissue extraction have been reported previously.[28] Young adult female Dutch rabbits weighing 1.5–2.0 kg. were used throughout this study.

Radiation Source and Exposure Data. Rabbits were irradiated in groups of 6 and given whole body exposures to 250 kv. roentgen rays from a Picker Industrial X-Ray Unit operated at 15 ma. at a distance of 100 cm., using aluminum and parabolic copper filters giving a beam with a half-value layer of 1.93 mm. Cu with an output of 10 r per minute. Animals were placed around the circumference of the field to insure uniform exposure in respect to radiation dosage and quality.

Particle Size Determination on the Colloidal Prodigiosin. Particle size determinations were made on representative samples of colloidal prodigiosin suspensions by using the electron microscope and shadow-casting techniques. Results showed that 89 per cent of the particles measured 0.05 μ or less in diameter and 11 per cent were between 0.1 and 0.05 μ. Larger particles appeared to be aggregates and were not measured. The crystalline prodigiosin was peptized with 0.5 per cent ascorbic acid and 2.5 per cent dextrose.

Techniques Used for Determining Prodigiosin Blood Retention—"Rationale and Pilot Studies." We have shown that colloidal prodigiosin is cleared from the blood within 15–20 minutes following intravenous injection.[23,24] The dye is not excreted in the urine, but is found in high concentrations in organs of the reticuloendothelial system.[24,25] This behavior is characteristic of other colloidal materials[10,11] and the rate of blood clearance in normal animals is primarily a function of particle size. Colloidal suspensions of large particle size disappear more rapidly (minutes) than those of small size (hours). When particle size, dosage and concentration of the dye are controlled, the rate of clearance from the blood or the amount of retention after fixed intervals is believed to de-

pend mainly on the function of the endothelial phagocytes of the reticuloendothelial system and to a lesser degree on the same function of the circulating leukocytes in normal rabbits. Therefore, depressed phagocytic function of these groups of cells should promote dye retention in the blood and their overactivity should be associated with accelerated blood clearance or decreased blood retention.

Dosage of Colloidal Prodigiosin. The standard dosage of dye employed in all except some preliminary studies was 1.3 mg/kg., using dye concentrations of approximately 1.0 mg/ml.

Procedures for Determining Prodigiosin Blood Retention. The standard dose of dye was injected into the marginal ear veins of female Dutch rabbits. A 5–10 ml. sample of blood was obtained by cardiac puncture 5 minutes after injection. This interval was selected after plotting the clearance curve from data on a large series of normal rabbits, wherein each animal was bled 1, 5, 10 and 15 minutes after injection.[24] This single sample technique was selected as a standard procedure because it avoided alteration of the circulatory dynamics and gave reproducible results.

The quantity of prodigiosin in the blood sample was then determined by a method previously reported.[28]

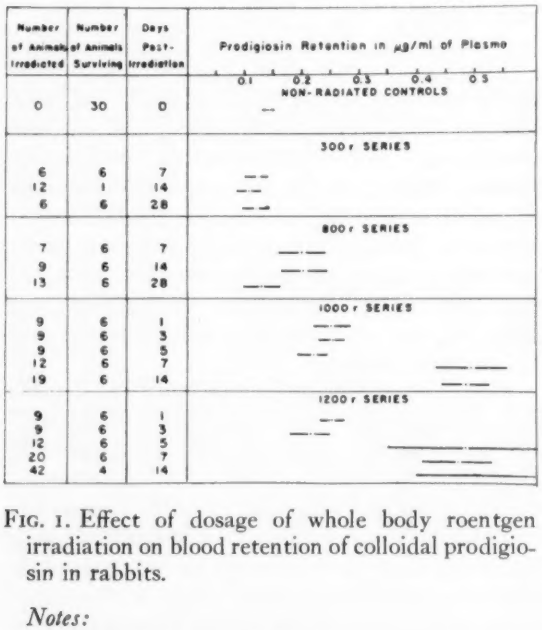

FIG. 1. Effect of dosage of whole body roentgen irradiation on blood retention of colloidal prodigiosin in rabbits.

Notes:

1. Dosage of prodigiosin—1.3 mg/kg. body weight.
2. Values shown for prodigiosin blood retention are the means ± the standard deviation computed from the formula:

$$SD = \sqrt{\frac{\Sigma\Delta^2}{n(n-1)}}.$$

RESULTS

I. *Effect of Dosage of Whole Body Roentgen Irradiation on Blood Retention of Prodigiosin in Rabbits.* In Figure 1, the values for blood prodigiosin retention are shown for normal and for irradiated rabbits given increasing doses of whole body roentgen irradiation. It is apparent that dye retention was slightly decreased temporarily by doses of 300 r. With 800 r exposures, the dye level increased, reaching a peak between the seventh and fourteenth days postirradiation, then decreased to levels below that of the controls by the twenty-eighth day after exposure. Following 1,000 r exposures, prodigiosin blood levels rose abruptly on the first day and reached three to five times the normal control values between the seventh and fourteenth days. In the 1,200 r series, a similar relation exists, differing only in respect to time. Significant increase in blood concentrations appeared within twenty-four hours and maximum blood levels were found after only five days.

II. *Organ Distribution of Intravenously Injected Colloidal Prodigiosin in Normal and Roentgen Irradiated Rabbits.* Data presented in Table 1 were accumulated from 126 separate rabbit experiments. Each animal was sacrificed fifteen minutes following the intravenous injection of 1.3 mg/kg. of colloidal prodigiosin. Values for prodigiosin content are presented in two ways, in micrograms per organ and in micrograms per gram of wet tissue. Spleen weights are recorded in grams of wet tissue. Prior to sacrifice, a blood sample was obtained by cardiac puncture exactly five minutes after the injection. These organ distribution studies were made in normal animals and in others given whole body radiation exposures in doses of from 300 to 1,200 r in order to determine whether the alterations in prodigiosin organ content could be related to variations in prodigiosin blood retention determined simultaneously during the first twenty-eight days postirradiation.

Interpretation of the organ distribution data is difficult. When comparison is made for each organ between the mean value from the 30 controls and the values for irradiated animals, there is no consistent difference in all of the

TABLE I

ORGAN DISTRIBUTION OF COLLOIDAL PRODIGIOSIN 15 MINUTES AFTER INTRAVENOUS INJECTION IN NORMAL AND ROENTGEN IRRADIATED RABBITS

Roentgen Radiation Dosage	Days after Irradiation	Lung, μg. prodigiosin		Liver, μg. prodigiosin		Spleen, μg. prodigiosin		Kidney, μg. prodigiosin		Skeletal Muscle, μg. prodigiosin per gram	Spleen Weight, gm.
		Per organ	Per gram	Per organ	Per gram	Per organ	Per gram	Per organ	Per gram		
300 r	7	48.0	6.2	438.2	7.8	7.9	16.5	11.0	2.3	0.03	0.48
	14	71.8	10.3	352.0	5.6	12.8	26.1	20.3	3.6	0.27	0.46
	28	75.9	10.3	435.4	7.7	18.0	26.1	20.3	3.5	0.00	0.64
800 r	7	189.5	30.0	100.1	1.9	5.6	17.7	19.4	2.8	0.000	0.30
	14	151.8	18.8	128.4	3.2	3.7	8.0	13.4	2.2	0.00	0.33
	21	265.0	34.0	182.3	2.2	7.5	17.7	24.5	3.8	0.00	0.50
	28					7.4	17.8				0.68
1,000 r	1	80.4	11.7	166.7	3.6	5.6	19.7	20.2	1.8	0.31	0.32
	3	96.2	17.8	144.1	3.6	3.6	19.4	6.3	1.2	0.18	0.18
	5	74.3	12.6	67.2	1.8	4.2	20.1	16.6	1.6	0.14	0.23
	7	78.3	14.3	79.4	2.0	4.2	26.9	10.8	1.1	0.22	0.18
	14	185.3	15.8	202.6	4.9	2.9	14.6	7.9	0.7	0.26	0.21
1,200 r	1	54.6	8.1	140.9	3.0	3.5	12.7	8.1	1.5	0.15	0.32
	3	144.5	19.1	269.7	6.0	3.4	11.9	15.5	2.6	0.14	0.27
	5	103.2	17.0	192.6	4.8	2.3	9.5	12.1	2.0	0.01	0.24
	7	150.3	25.3	268.6	6.6	2.3	7.1	12.5	2.5	0.11	0.26
Nonirradiated Controls		79.9	10.6	202.3	4.7	10.16	16.25	14.88	2.6	0.026	0.63
		±7.05	±1.7	±20.1	±0.38	±1.74	±1.18	±2.68	±0.36	±0.006	±0.21

Notes:

(1) Each value is the average computed from data on 6 separate animals.

(2) Dosage prodigiosin = 1.3 mg/kg. body weight.

(3) Irradiation factors: 250 kv. whole body roentgen irradiation with half-value layer 1.93 mm. Cu delivered at 10 r/min.

(4) In each series, at least 6 animals were used as controls. Total number of controls: 30.

(5) Standard deviation values given for nonirradiated controls were computed by use of the formula: $SD = \sqrt{\frac{\Sigma\Delta^2}{n(n-1)}}$.

major reticuloendothelial organs at any specific postirradiation interval or dosage level. It was anticipated that there would be a definite inverse relation between reticuloendothelial organ content of prodigiosin and blood retention. For example, one would expect that a decrease in spleen-liver content would accompany the rise in blood prodigiosin retention following large doses of radiation. One might then attribute the abnormally high blood retention to decreased ability of the major reticuloendothelial organs to perform their filtering functions. It is likely that the difficulty of demonstrating such clean-cut relationships is due to a number of factors, such as normal biological variation, blood and plasma volume changes,[22] alteration in capillary permeability, technical error in extraction and measurement,[28] slight variation in particle size distribution from one batch of prodigiosin to another and to the relatively small number—6—of animals in each experimental group.

However, some general trends are apparent from the data (Table 1) which fit with the basic hypothesis:

1. Values for prodigiosin content in the livers and spleens of irradiated animals given 800 r or larger exposures are generally lower than for controls on both an organ and on a per gram basis, especially during the first two weeks postirradiation. By the twenty-eighth day, these values return to levels within the normal range.
2. Prodigiosin values in kidney and muscle tissues are not altered significantly in either direction at any time after irradiation.

The prodigiosin content in lung tissue of irradiated rabbits is generally higher than that in controls except in the 300 r series, where the levels remain within normal limits during the entire twenty-eight day postirradiation period. The fact that liver and spleen values in the 300 r

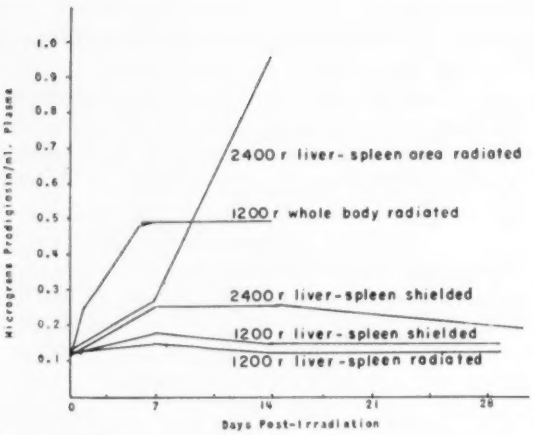

FIG. 2. Effect of lead shielding the major and minor parts of the reticuloendothelial system on the retention of prodigiosin in the plasma of roentgen irradiated (1,200 and 2,400 r) rabbits.

Notes:

1. Each value shown represents the mean from determinations on six separate animals.
2. Radiation factors: 250 kv. roentgen radiation, 15 ma., half-value layer 1.93 mm. Cu at a rate of 10 r/minute.
3. The liver-spleen areas were shielded during irradiation by 2.5 mm. of lead.
4. In the liver-spleen irradiated animals, the remaining body surface was shielded with 2.5 mm. lead

series are definitely higher than in the controls throughout the same postirradiation period is indicative of hyperactive phagocytic function. These findings are consistent with the observations of Bloom[3] in splenic tissues of irradiated rabbits.

3. Finally, the data on spleen weights demonstrate a number of interesting relationships. First, there is a good correlation between reduction in spleen weight and radiation dosage. Second, this reduction in spleen weight occurs more rapidly with larger doses. Third, spleen size returns to normal in animals surviving twenty-eight days following 300 and 800 r exposures. Fourth, spleen weight continues to decrease with time in animals surviving higher doses (1,000 and 1,200 r). These findings agree with the postulated alteration of reticuloendothelial system phagocytic function following radiation exposure, as measured by changes in blood prodigiosin retention.

III. *The Effect of Shielding the Major Portion of the Reticuloendothelial System during Roentgen Irradiation on Blood Retention of Prodigiosin.* It was postulated that if the reticuloendothelial cells in the liver and spleen, which constitute 90 per cent or more of the total reticuloendothelial system, were protected during roentgen irradiation by sufficient shielding (2.5 mm. Pb), the blood levels of prodigiosin should remain in the normal range. Results from the 1,200 r series, presented in Figure 2, indicate that this hypothesis was correct.

Conversely, local exposure of the liver-spleen areas with the remaining body surface shielded should be associated with increased dye retention in the blood. Findings shown in Figure 2 for the 1,200 r series demonstrate that prodigiosin levels are slightly increased and, in addition, mortality in this series was only about 10 per cent.

When these experiments were repeated using 2,400 r doses, prodigiosin levels in the liver-spleen exposed group rose rapidly and actually surpassed those found in the 1,200 r series given whole body irradiation. Likewise the mortality in fourteen days was about 90 per cent. Conversely, in the 2,400 r liver-spleen shielded group, prodigiosin blood concentrations increased to approximately twice the normal values and only about 15–20 per cent of these animals succumbed during the first twenty-eight days postirradiation, again demonstrating the importance of protecting the reticuloendothelial system during radiation exposure.

IV. *Dye Retention Studies in Rabbits Having Chloroform-Induced Liver Damage.* Severe liver damage was produced in rabbits by tube feeding them daily with 2 ml. of cottonseed oil containing 20 per cent chloroform for four days. When gross evidence of jaundice occurred, the animals were tested for both bromsulfalein and prodigiosin retention.

Results shown in Table II demonstrate that chloroform-induced portal liver area injury is followed by a definite increase in both prodigiosin and bromsulfalein retention. However, the increase in bromsulfalein retention is greater than that for prodigiosin.

V. *Effect of India Ink Blockade on Prodigiosin and Bromsulfalein Retention.* Rabbits were given daily intravenous injections of India ink containing 10^{13} particles per ml., in doses of 1.0 mg/kg. body weight for four days. One hour following the fourth injection, bromsulfalein and prodigiosin retention tests were performed. Results presented in Table III show that blockaded animals had moderately

Table II

EFFECT OF CHLOROFORM-INDUCED LIVER DAMAGE IN RABBITS ON PLASMA RETENTION OF BROMSULFALEIN AND PRODIGIOSIN

No. Animals	Average Weight (grams)	Per Cent Bromsulfalein Retained		No. Animals	Average Weight (grams)	Prodigiosin Retention, μg/ml. 5 min.
		5 min.	30 min.			
5 Controls	1,470	93.2±30	79.7±2	4	1,260	0.84±0.1
15	1,500	15.4± 1.5	5.2±1.5	40	1,450	0.14±0.01

Notes:

Dosage (1) Bromsulfalein—5 mg/kg. body weight.
(2) Prodigiosin—1.3 mg/kg. body weight.
(3) Chloroform—2.0 ml. of 20 per cent solution in Wesson oil fed by tube daily for 4 days prior to test.
(4) Values for plasma retention are the means ± the standard deviation $= \sqrt{\frac{\Sigma\Delta^2}{n(n-1)}}$.

increased blood retention of both bromsulfalein and prodigiosin with levels about two to three times higher respectively than those found in normal controls.

VI. *Effect of 1,000 r Whole Body Roentgen Irradiation on the Bromsulfalein Retention in Rabbits.* Data presented in Table IV demonstrate that the blood retention of bromsulfalein is not increased in rabbits given 1,000 r whole body roentgen irradiation exposures. In fact, results obtained from animals tested five to fourteen days postirradiation show lower values than those found in nonirradiated controls. These findings indicate that this dosage of radiation is insufficient to induce polygonal cell dysfunction, detectable with the bromsulfalein dye excretion test. Prodigiosin retention, however, is significantly increased under similar circumstances, indicating that functional impairment of the phagocytic activity in the reticuloendothelial system had most probably been induced.

VII. *Effect of 1,000 r Whole Body Roentgen Irradiation on Prodigiosin Blood Retention in Normal and India Ink Blockaded Animals.* These experiments were conducted to determine how rabbits having reticuloendothelial system blockade withstood radiation exposure with normals, and whether or not the added insult to the reticuloendothelial system from radiation exposure was followed by further increases in plasma prodigiosin retention. Data shown in Table V demonstrate that the prodigiosin blood levels twenty-four hours postirradiation are significantly higher in the group previously given India ink reticuloendothelial sys-

Table III

EFFECT OF INDIA INK BLOCKADE OF THE RETICULOENDOTHELIAL SYSTEM ON BROMSULFALEIN AND PRODIGIOSIN RETENTION IN THE PLASMA OF RABBITS

No. Animals	Average Weight (grams)	Per Cent Bromsulfalein Retained		No. Animals	Average Weight (grams)	Prodigiosin Retention, μg/ml. 5 min.
		5 min.	30 min.			
5	1,590	50.0±6.5	8.0±1.0	7	1,500	0.22±0.04
Controls 15	1,500	15.4±1.6	5.2±1.5	30	1,450	0.14±0.01

Notes:

Dosage (1) Bromsulfalein—5 mg/kg. body weight.
(2) Prodigiosin—1.3 mg/kg. body weight.
(3) India ink—1 ml/kg. body weight of a 1:5 dilution of Higgins ink for 2 days and 1–2 hours prior to testing on the test day.
(4) Values shown for dye retention are means ± standard deviation $= \sqrt{\frac{\Sigma\Delta^2}{n(n-1)}}$.

tem blockade than in any of the accompanying control series. These findings further substantiate the hypothesis that mid-lethal and/or larger doses of whole body roentgen radiation cause impairment in phagocytic function of the macrophage system. Furthermore, the data also presented comparing spleen weights in each of the groups indicate that India ink may promote proliferation in the reticuloendothelial system in addition to its blocking effect.

TABLE IV

EFFECT OF 1,000 r WHOLE BODY ROENTGEN IRRADIATION ON THE PER CENT RETENTION OF BROMSULFALEIN IN THE BLOOD OF RABBITS

No. Animals	Mean Weight (grams)	Per Cent Dye Retention	
		5 min.	30 min.
	(5–7 days postirradiation)		
15	1,165	14.3±1.8	3.4±0.6
	(9–14 days postirradiation)		
10	1,280	13.9±1.0	3.0±0.4
	(Nonirradiated controls)		
15	1,450	15.4±1.5	5.2±1.5

Notes:

(1) Dosage: Bromsulfalein—5 mg/kg. body weight.
(2) Values shown for dye retention are means ± standard deviation.

DISCUSSION

The authors are cognizant of the complexity of the problems involved in evaluating phagocytic function in organs of the reticuloendothelial system. Perusal of the pertinent literature on this subject discloses that many others have encountered similar difficulties and variable findings.[1,2,5,9,13,16,20,21] One of the major problems is related to the wide range of activity and tremendous reserve capacity of this system. Thus, to demonstrate depressed function, one must overcome this reserve. Furthermore, organs of the reticuloendothelial system have great regenerative ability, and this factor must be considered in experiments designed to produce reticuloendothelial system blockade. From our studies, it is apparent that one could readily arrive at diametrically opposed conclusions, depending either on the time at which the observations were made in respect to the irradiation-induced changes in phagocytic function or on failure to use higher than mid-lethal doses of radiation. However, by performing similar experiments at several time intervals and after a wide range of radiation dosage, it has been possible to demonstrate quite conclusively that large doses (800–1,200 r) of whole body roentgen

TABLE V

EFFECT OF 1,000 r WHOLE BODY ROENTGEN IRRADIATION ON BLOOD RETENTION IN NORMAL AND INDIA INK BLOCKADED RABBITS

Type Animal	Number of Animals	Prodigiosin Blood Retention, μg/ml.		Mean Spleen Weight (grams)
		5 min.	15 min.	
Normal controls	50	0.14±0.01	0	0.63±0.21
India ink blockaded controls	6	0.18±0.02	0	1.28±0.07
Irradiated controls	6	0.25±0.03	0.05±0.02	0.31±0.02
Irradiated India ink blockaded animals	4	0.83±0.03	0.34±0.01	0.95±0.20

Notes:

(1) Rabbits were administered daily intravenous injections of Higgins brand ink for 5 days, 1 ml/kg. of a 1:20 dilution.
(2) Of the 6 blockaded animals irradiated 6 hours after the last India ink injection, 2 died within 4 hours.
(3) Prodigiosin blood retention tests were performed 30 hours after the last injection of India ink in both the irradiated and nonirradiated blockaded groups.
(4) Blood samples were obtained by cardiac puncture, 5 and 15 minutes after injection of 1.3 mg/kg. of prodigiosin intravenously.

irradiation are followed by either a temporary or permanent depression of phagocytic function in the macrophage system, whereas lower doses (300 r) gave relatively insignificant changes in this function. At the 800 r level of radiation exposure, phagocytic function is temporarily depressed for about seven to ten days and, during the next ten to twenty days, there is evidence of complete recovery, similar to the so-called rebound phenomenon known to occur following other forms of injury to tissue. Our findings may augment the existing theories[15] by which the beneficial effects of therapeutic doses of radiation exposure are explained. Furthermore, these results demonstrate that the macrophage system is far more important than the circulating leukocytes in clearing the blood stream of insoluble fine particles including avirulent bacteria, because whole body irradiation with doses in the 300–400 r range are known to cause severe leukopenia during the first two weeks postirradiation.[12] Therefore, in respect to resistance against sepsis from the bacteria normally inhabiting the gastrointestinal tract, it is likely that measurement of macrophage function may well be of greater diagnostic and prognostic significance than the usual morphological studies on the circulating leukocytes. This deduction is further supported by the findings of Bloom that leukocytes in irradiated rabbits rapidly become nonphagocytic and soon degenerate, at which time they are regularly engulfed by the more radioresistant macrophages.

Nevertheless, there still remain a number of factors which could influence the rate of removal of colloidal prodigiosin from the blood other than the phagocytic activity of the macrophages. First, although prodigiosin has been shown to remain in colloidal form when added to rabbit blood, one cannot be certain that aggregation of particles does not take place in vivo. Also, increases in capillary permeability and sizeable alterations in blood and plasma volumes[22] with associated alterations in circulatory dynamics are known to occur during the first weeks in the acute radiation syndrome. Finally, the initial removal of fine particles from the circulating blood is also accomplished by their mechanical adherence to capillary walls. However, it is believed that the control studies performed in all of these investigations minimize the possible influence of those factors on our interpretations. In fact, increased capillary permeability and the expanding plasma volume[22] known to occur after lethal radiation exposures actually increase the significance of our high values for prodigiosin retention, because these factors would accelerate the rate of blood clearance or tend to lower the values for plasma retention. Furthermore, if colloidal prodigiosin became aggregated during its circulation, the larger size of such clumps would promote an increase in the rate of its removal from the blood stream.

In spite of a lack of clear-cut organ distribution results (Table 1), the overwhelming majority of the data presented demonstrates that the blood retention of intravenously injected colloidal prodigiosin may be used as a fairly sensitive index of phagocytic function of the macrophage system in rabbits. Doses of whole body roentgen irradiation in the 300 r range are not followed by significant changes in prodigiosin retention, and the mortality in rabbits given this amount of radiation is usually less than 10 per cent. Also, bacteremia seldom occurs at this dosage level, indicating that the reticuloendothelial system and other defenses have not been overcome.

After 800 r doses of whole body radiation the mortality in rabbits is about 50 per cent in thirty days. Most of the deaths occur between the fifth and fifteenth days. During this period there is depressed macrophage function, reduced spleen weight associated with cellular inactivity, along with granulopenia and evidence of bacterial infection. Sepsis occurs in a small percentage of cases. During the fifteenth to twenty-eighth days postirradiation (800 r), few animals die, splenic cellular activity

and weight return to normal, and phagocytic function of the macrophages likewise improves to levels equal to or above those in normal controls.

Rabbits given larger doses (1,000 and 1,200 r) of whole body roentgen irradiation die mainly either during the first twenty-four hours or between the fourth to tenth days. Only about 10 per cent survive longer than fourteen days. Animals given these lethal exposures have rapidly increasing prodigiosin blood retention, persistently small spleens, and evidence of toxicity, infection and sepsis prior to death. In similar animals given a 1,200 r whole body radiation exposure except over the lead shielded liver-spleen-spine area, the mortality is less than 10 per cent. There are also fewer toxic type deaths during the first twenty four hours after irradiation. Spleen weight is not so greatly reduced and prodigiosin blood retention remains within upper normal limits during the entire first month postirradiation. From these findings in liver-spleen shielded versus the nonshielded animals, it is evident that a normally functioning reticuloendothelial system is a major defense against the lethal effects of whole body exposure to radiation in rabbits.

The effects of chloroform-induced liver damage and India ink blockade on phagocytic function, as demonstrated by increased bromsulfalein and prodigiosin retention, provide substantiating evidence that whole body irradiation in the 800–1,200 r dosage range may cause a reduction of phagocytic function in the liver and in other organs of the reticuloendothelial system. However, the fact that 1,000 r radiation exposures fail to cause increased bromsulfalein retention indicates that this dye is handled differently and mainly by cells other than those of the Kupffer type in the liver, as has been postulated by others in studying dye excretion liver function tests.[19] Our comparative data on bromsulfalein and prodigiosin retention in rabbits with India ink blockade and with chloroform induced portal area liver damage indicate that bromsulfalein retention is greater in animals with polygonal cell liver injury than in those with Kupffer cell blockade. Although the same relation exists with prodigiosin retention, the magnitude of the retention of this dye is lower than that for bromsulfalein in both of these forms of liver impairment. In irradiated animals the reverse situation occurs, the retention of prodigiosin being a much more sensitive index of phagocytic function in the macrophage system than that of bromsulfalein. The final explanation for this difference must await the results of further investigation. However, sulfonated phthalein dyes are more soluble in tissue fluids,[19] and are therefore not taken up preferentially by phagocytic cells, as is the case with colloidal prodigiosin.

Potential Applicability of the Prodigiosin Blood Retention Test. There are numerous practical and experimental uses for a reliable method of determining phagocytic function in the macrophage system. Such a test is likely to be a useful tool in evaluating the role of the reticuloendothelial system in respect to the susceptibility to and the recovery from numerous infectious diseases of both viral and bacterial origin, in conjunction with immunological studies. Also, it could provide valuable information concerning the role of phagocytosis in the clearance of inhaled foreign material from the respiratory organs, thereby being helpful in the study of the inhalation hazards in industry, atomic warfare, and in certain allergic disorders of the respiratory organs. The investigation of drugs thought to be either depressant or stimulating to this function of the macrophage system could be evaluated first in laboratory animals, and only those drugs showing promise need then be submitted for clinical trials.

Because reticuloendothelial system functions are so important in respect to the resistance of animals to the effects of radiation injury, a colloidal dye similar to prodigiosin should be found which is more suitable for use in clinical medicine. Prodigiosin in its present dosage form, unfortunately, cannot be used repeatedly in

man for one reason. It has a sclerosing action on the lining of the peripheral veins, resulting in thrombosis within twenty-four to seventy-two hours. If another preparation of crystalline prodigiosin could be prepared which did not have this sclerosing property, it would be directly applicable in clinical research, because prodigiosin exhibits no other significant toxic action.

In the search for suitable substitutes for prodigiosin, another desirable feature of the ideal dye would be one with a chemical structure having firmly bound iodine in the molecule, so that the dye could be tagged with I^{131} or other gamma-ray emitting isotopes. The distribution of the tagged dye could then be followed throughout the body by use of external measurements made with a collimated gamma scintillation counter,[6] thus permitting the recording of variations in dye concentrations in the blood or reticuloendothelial organs in a dynamic fashion. Thereby, much more information could be obtained concerning reticuloendothelial function with less difficulty and with fewer animals, or with less discomfort to patients during clinical investigations. Preliminary studies using tagged particles are being made and the dyes tetraiodophenolphthalein[19] and rose bengal[8] appear to be suitable for tagging experiments.

Investigations are now in progress to demonstrate further that resistance or susceptibility to large doses of radiation is related to the state of phagocytic function in the cells of the reticuloendothelial system or to its degree of proliferation. Preliminary findings suggest that it may well be possible to reduce the mortality from or increase the tolerance to large doses of whole body irradiation by the prophylactic administration of reticuloendothelial system stimulants such as purified bacterial pyrogens, vaccines, foreign proteins and nontoxic colloidal materials. Furthermore, similar studies are in progress to determine whether these functions of the macrophage system may be stimulated *after* radiation injury has been sustained.

SUMMARY

1. The retention of intravenously injected colloidal prodigiosin in the blood has been demonstrated to be an index of phagocytic function in the reticuloendothelial system of rabbits.

2. Phagocytic function of the circulating granulocytes plays a relatively minor role in the clearance of colloidal prodigiosin particles from the blood of heavily irradiated rabbits, compared with that of the macrophages.

3. Whole body 250 kilovolt roentgen irradiation in the dosage range of 800–1,200 roentgens is followed by highly significant increases in the retention of prodigiosin in blood plasma, indicating a depression of phagocytic function in the macrophage system or a temporary arrest of its ability to regenerate.

4. Determination of prodigiosin blood retention may be helpful in estimating the degree of whole body radiation injury and in predicting the onset of recovery following a single exposure to mid-lethal or higher doses.

5. Protection of either the major or minor organs of the reticuloendothelial system *during* lethal (1,200 r) radiation exposure of rabbits by lead shielding results in greatly reduced mortality, decreased radiation toxicity and in maintenance of normal phagocytic function in the macrophage system as a whole.

6. Chloroform-induced portal area liver damage and India ink reticuloendothelial system blockade are both followed by increases in prodigiosin and bromsulfalein blood retention in rabbits.

7. Prodigiosin is far more sensitive than bromsulfalein as an index of depressed phagocytic function in the macrophage system of rabbits following 800–1,200 r doses of whole body roentgen irradiation.

8. Bromsulfalein blood retention is increased more by chloroform-induced portal area liver damage than by reticuloendothelial system blockade with India ink.

9. Prodigiosin in the form used in these studies (colloidal particles peptized with

ascorbic acid and glucose) is not suitable for repeated injections in patients because it uniformly causes phlebothrombosis at the site of injection.

10. It is believed that the findings presented may lead to a better understanding of the mechanism of the bacterial complications following radiation injury in rabbits.

11. It is suggested that prophylactic administration of agents known to stimulate macrophage proliferation or phagocytic function, in addition to other forms of supportive therapy, may lead to greater success in the management of the acute radiation syndrome.

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COMPARATIVE EFFECTS OF COBALT 60 AND RADIUM WHEN UTILIZED IN IDENTICAL DOSES ON THE SKIN OF RABBITS*†

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A BASIC technique has been established for the utilization of cobalt 60 as a radium substitute, in a manner similar to previous established methods for the utilization of radium.[4]

Sixteen gauge hyperchrome steel tubing‡ has been utilized as a sheath for irradiated cobalt wire 1 mm. in diameter. The needles can be made to any desired lengths with an eyelet bored at one end of the sheath previously crushed and the other end closed with silver solder. The absorber equivalent of this sheath is approximately twice the calculated necessary thickness to filter out all of the beta rays from cobalt 60 which have a maximum energy of 0.310 mev. A method of standardization of these needles against a standard solution furnished by the National Bureau of Standards has been described.[4]

The original dosage table presented was based upon the roentgen equivalency of cobalt 60 in terms of milliroentgens per hour at 1 meter (mrhm.)—namely 1.30 mrhm. for 3.7×10^7 disintegrations per second. This dosage table was obtained by multiplying Paterson-Parker values by the factor 0.646, which is the ratio of 0.84 to 1.30. More recently, a more correct knowledge of the disintegration scheme of cobalt 60 would make this ratio: $0.84/1.356 = 0.619$, and the newer tables have been presented for publication.[6]

These tables are applicable for any molds or interstitial cobalt 60 implants for uniplanar distributions in accordance with established Paterson-Parker rules.

As pointed out previously, the gamma-ray spectrum derived from the decay of radium 226 is very complex, but its average energy is approximately 0.78 mev.[2] The average from cobalt 60 is 1.2 mev. The comparative effects biologically of these two different qualities of radiation as well as the applicability of the converted Paterson-Parker tables must be established before one can utilize cobalt 60 radiation optimally. In a previous article[5] the results of experiments were described in which the biologic effects of these hyperchrome steel needles were compared with radium needles of a similar low intensity type, 2 by 2 cm. areas on the skin of rabbits were implanted with cobalt 60 hyperchrome steel needles on the left side of the abdomen and a similar area on the right side of the abdomen was implanted with radium needles. It was our purpose in these experiments to compare the cobalt 60 needles as we intended to use them with the radium methods with which we are familiar. In interstitial experiments of this type it is virtually impossible to control several of the important factors. Since, however, in two-thirds of the experiments the cobalt 60 reactions seemed more severe than the radium, and the differences seemed greater than the known variables could account for, it was our next purpose to devise a series of experiments in which every variable would be controlled.

‡ Becton, Dickinson Company, Rutherford, New Jersey.

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The results obtained from this series of interstitial experiments were interpreted with considerable caution because of the several uncontrollable variables: (1) In interstitial implantation experiments it is virtually impossible to implant identical areas, particularly in a rabbit where a loose subcutaneous layer exists. However, the differences in area were not very great and in every case they were indicated by roentgenographic studies following implantation. (2) The distance "*h*" of irradiation might also vary slightly in interstitial skin implants since the needles must be imbedded in the loose subcutaneous layer on both sides of the abdomen. In a given animal it is not likely that the implants will vary significantly in depth on the two sides of the abdomen, particularly in rabbits' skin, since the needles practically fall into position in this subcutaneous layer. Nevertheless, a series of experiments would be desirable in which the factor "*h*" and also the area could be better controlled than in these interstitial experiments. (3) One of the most important variables that could not be controlled in these interstitial experiments was the "time factor." It has been repeatedly shown that the duration of irradiation and the dose rate are both significant as compared with the life of the cells concerned. Cohen[1] and also Strandqvist[10] have shown that radiation effects resulting from unequal periods of irradiation are related to one another by the formula: dose $(\text{time})^n$, where the exponent "*n*" is different for different tissues. In the case of the normal skin, Cohen has indicated a value of 0.33 for *n*, and Strandqvist a value of 0.22 for *n* for squamous cell carcinoma. Reisner's[9] data for human skin erythema indicates *n* for normal skin to be 0.3.

It was indicated that the time differences, although small in the interstitial experiments, might still be significant in causing differences in observable radiation reactions, but that these results were still of importance since such time differences frequently occur in clinical applications.

It was desirable to devise a series of experiments in which the time factor could be virtually eliminated. It has been demonstrated that if fractionated dosage is employed, the actual dose rate may differ somewhat, provided the over-all dosage time is identical and provided the dose rate differences are not excessive (McWhirter, 1936;[3] Quimby and MacComb, 1936[7]). If, therefore, one can apply the cobalt and radium radiation externally, and if the over-all time of irradiation remains the same, small fractionation differences will not interfere significantly in the biological effect, provided the dose rates are virtually identical. In the series of experiments to be described below such a method was devised for keeping the time factor virtually constant for the two types of radiation modalities. The time factor was controlled by fractionating the radium irradiation since the cobalt 60 wire was of somewhat lower equivalent intensity than the radium emanation. An over-all irradiation time of between 144 and 150 hours was employed in this series of experiments, the radium being removed midway in the treatment time for a period of several hours so that the over-all treatment time of both the cobalt and the radium would ultimately be identical. This has been accepted as a satisfactory technique for keeping the over-all radiation time identical, provided the dosage rates are not excessively different. Since they were not excessively different in this instance we can therefore consider that the time factor was constant in both series of experiments.

(4) Superimposed infection or trauma was controlled in this series of experiments by devising a lead shield which completely surrounded the rabbit's abdomen and prevented him from traumatizing his skin during the period when such trauma was most apt to occur. Traumatized irradiated areas were therefore not very frequently encountered and were not a serious problem in this series of experiments. Also, the animal or individual differences were completely overcome by the fact that the two

irradiated areas were identical areas on the two sides of the abdomen of the same rabbit. There was a fair amount of variation from animal to animal, and hence if one were to utilize only one modality of radiation in a single animal one would require a very large series of animals to obtain similar observations. Since the two qualities of radiation were always observed as they affected the same animal, this variable was completely overcome and it was calculated that the cross effects of one modality of radiation onto the opposite area would be less than 5 per cent, and hence insignificant.

(5) Another variable which was not controlled in the series of interstitial experiments reported previously was that of the construction of the needles themselves. Although the active lengths of the radium needles were 16 mm. and their over-all lengths 25 mm., the active lengths of the cobalt needles were 20 mm. and the over-all lengths 22 mm. According to Parker, this slight difference in active lengths should not make a significant difference when the *areas implanted* were 2 by 2 cm., and the distance between the needles did not exceed "*h*."* However, the construction of the needles was another factor. In the case of the cobalt needles, a hyperchrome steel sheath was employed which had a wall thickness of 0.23 mm.; whereas the radium was ensheathed in platinum with a wall thickness of 0.5 mm. The over-all diameters of the two needles were virtually identical. Nevertheless, it was conceivable that there might be differences in secondary radiation immediately around the needle and also slight differences in oblique filtration which must be taken into account. Although physical studies of the hyperchrome steel needles as against the platinum ensheathed radium needles revealed no significant differences in the secondary beta radiation, and, if anything, should theoretically be less for steel than for platinum;[8] and although photometric studies of the isodose curves obtained from plaques constructed with the hyperchrome steel needles compared with the platinum ensheathed radium needles were identical,[5] it was still deemed advisable to attempt to compare the radiation of the cobalt 60 with the radium when the cobalt 60 was ensheathed in identical fashion to that of the radium.

On the basis of the above slight variables in the interstitial experiments, two series of experiments were devised and performed in which these variables were virtually completely overcome. In the first series, the cobalt needles were constructed in identical fashion to the radium needles with the exception that gold was substituted for platinum and the cobalt wire was ensheathed by gold 0.5 mm. in thickness. The active length of the cobalt wire was exactly the same as that of the radium, as was the over-all length of the needles. Plaques made of masonite presdwood were thereafter constructed in which both the cobalt needles and the radium needles were imbedded so that a 2 by 2 cm. area would be irradiated. These plaques were constructed identically so that the distance of irradiation was identical in both instances.

In the second series, the original hyperchrome steel needles replaced the gold.

Since the differences in results between these two series was minimal, they will be discussed together.

EXPERIMENTAL METHOD

The detailed technique was as follows:

(1) The hair was clipped from the entire abdomen of the rabbit.

(2) The radium plaque was applied on the right side of the rabbit's abdomen and the cobalt plaque applied in an identical area on the left side of the abdomen so that the separation of the two treatment areas was a minimum of 6 cm. The plaques were thereafter covered with a light layer of gauze moistened with collodion which sealed the plaques in position on the abdomen.

* Actually, Parker recommends that needles be crossed at their active ends. We have varied from this recommendation by a distance not exceeding "*h*" and find that it is probably inconsequential. In the above experiments (Series 1), this factor was the same for both the radium and cobalt.

Construction of Plaques. The plaques were made of masonite presdwood with over-all dimensions of 4.4 by 4.4 cm. and 8 mm. thickness (Fig. 1). Grooves were cut in the upper surface of these blocks to permit the imbedding of the needles, making a treatment area of exactly 2.0 by 2.0 cm. The ends of the needles were to be crossed in identical fashion and the center was measured to the mid-section of the two layers of needles, and it was found by experiments in dosage that to obtain a good reaction in six or seven days, the distance "*h*" would have to be 2.5 mm. from the treatment surface.

The radium needles employed were the same as those described previously. The periphery of the square was formed by 2.0 mg. needles having an active length of 1.6 cm., and an over-all length of 2.5 cm., and casing of 0.5 mm. platinum. The central needle was a 1.0 mg. needle of identical construction.

In Series I the cobalt needles were reconstructed as follows: Their active lengths were reduced to 16 mm. and the cobalt wire was placed inside a gold casing whose over-all length was 2.5 cm. and wall thickness 0.5 mm. As of July 1, 1950, the strength of the peripheral needles was 1.2 mc. each, and the central needle was 0.6 mc. These needles therefore were virtually identical in construction to the radium needles. It was estimated from absorption curves that a 3 per cent correction would be made for the attenuation of the gamma rays by the gold casing.

In Series II, the hyperchrome steel encased needles were employed in identical areas (but needles crossed at active 2 cm. ends).

In every instance the radium radiation had to be fractionated so that the over-all treatment time would be identical, and hence the radium plaque was removed approximately midway in the treatment period and reapplied in the identical area so that the over-all treatment time would be the same. The cobalt plaques, however, did not have to be removed and remained in position throughout the treatment period calculated to deliver 7,000 gamma roentgens. After the plaques were applied, the entire area was covered by a lead shield which virtually immobilized the animal. (The scatter from the lead would not affect the treatment areas, since these beta rays would be absorbed in the first millimeter of the plaque covering the treatment areas.) This, in turn, was bound by a sufficient roll bandage so that the treatment areas could not be traumatized in any way by the rabbit.

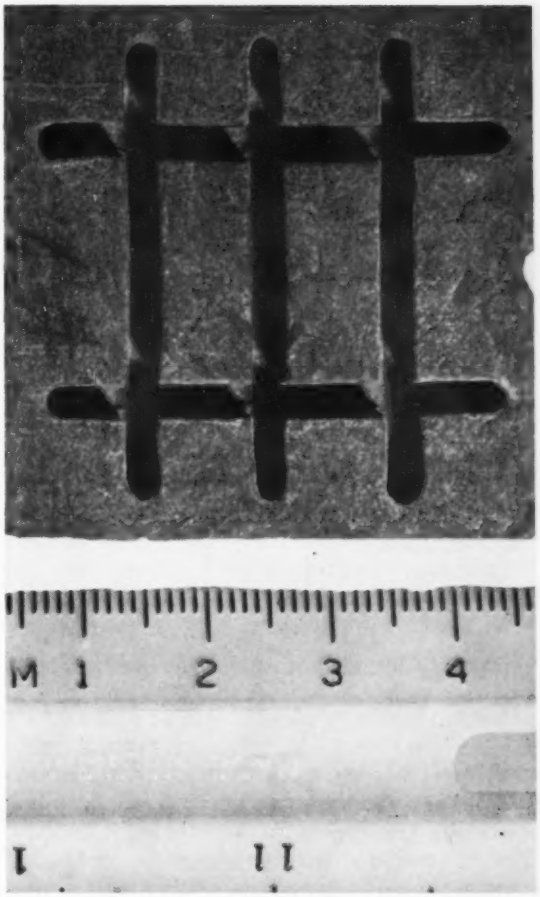


Fig. 1. Masonite presdwood plaques utilized in these experiments.

After 7,000 gamma roentgens had been delivered (calculated as 0.5 cm. "*h*" or 0.25 cm. beneath the skin surface), the plaques were removed and the treatment areas were bandaged with a 5 yard roll thereafter until the maximum reaction had subsided and the treatment area was healed. It was noted that, once the treatment area had healed, the animal was not very apt to traumatize the treatment area.

In order to obtain a readily comparable reaction on the two sides, after considerable initial experimentation with dosage it was decided to employ the 7,000 gamma roentgens as calculated to a layer 0.25 cm. beneath the surface of the skin. This, of course, would mean that a considerably larger dosage was obtained at the skin surface proper (approximately 10,500 r, extrapolating Paterson-Parker tables), but in each instance the dosage levels administered were the same for the two sides of the animal

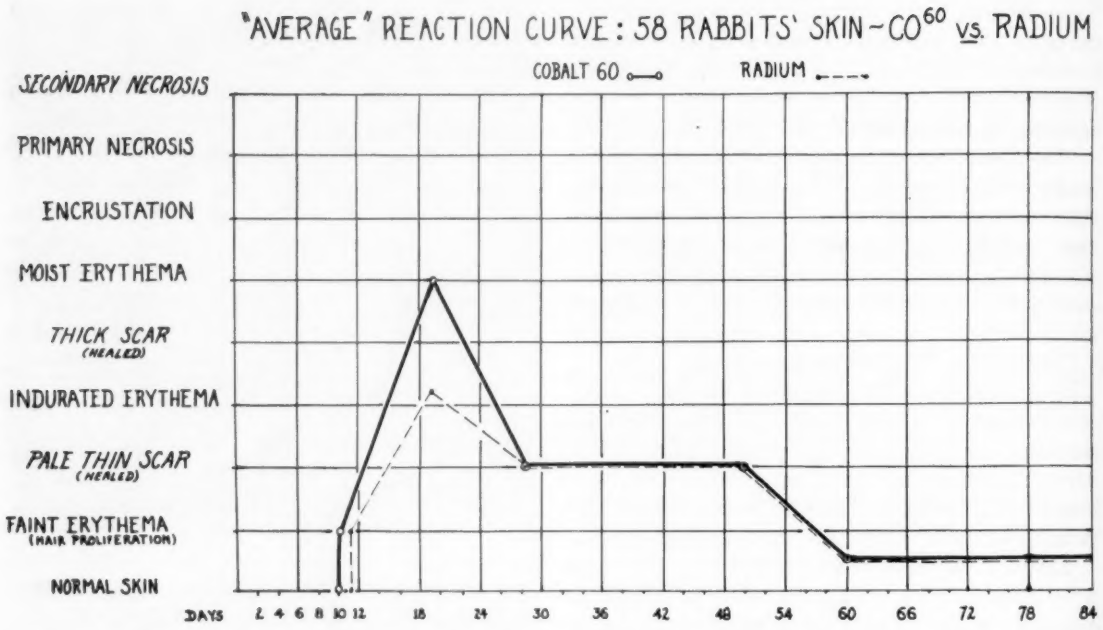


FIG. 2. Graphic presentation of the average reactions obtained from cobalt 60 and radium applied in identical dosages to the two sides of rabbits' abdominal skin in areas of 2 by 2 cm. in 144 to 150 hours. (Over-all time identical for the two sides in each application.) Fifty-eight rabbits in gross series; 13 in microscopic series.

since the calculations and the construction of the plaque were the same on both sides.

For the purpose of gross pathologic description the treated areas were observed at frequent intervals, proper notations made, and Kodachrome photographs obtained at appropriate time intervals when notable changes occurred. The areas were carefully studied from the standpoints of: primary erythema intensity and area; induration; moist erythema intensity; primary healing; character and size of the healed scar; secondary breakdown of the healed scar; when and whether secondary healing occurred. After three to four months when a stationary state had been reached, the recorded observations and descriptions were transferred to a graphic plotting of the reaction so that ready comparison of the cobalt reaction could be made as against the radium reaction.

Each animal was virtually its own control, since identical areas were employed on the two sides of the same rabbit; and these areas were treated in identical fashion with the exception that cobalt needles were embedded in one plaque and radium needles were embedded in the other. A total of 30 rabbits was studied grossly in Series I; and 28 rabbits in Series II.

For the purpose of microscopic study, a total of an additional 13 rabbits was studied in Series I. The entire treatment areas were removed for biopsy at certain specified intervals following the removal of the plaques, and the center of the area cut with a scalpel so as to mark it clearly. The time intervals studied were as follows:

1 week	3 rabbits
2 weeks	4 rabbits
3 weeks	4 rabbits
4 weeks	2 rabbits

Four sections were made from each biopsy site, and stained by hematoxylin and eosin techniques only, since in our previous study we found this method to give maximum results.

In our previous microscopic studies[5] we did not find the study of the healed scar helpful from the standpoint of comparing the two modalities of radiation, and this phase of the study was omitted at this time.

Greatest emphasis was placed on the one to three week interval following irradiation on the basis of the observations made in our interstitial experiments.

DESCRIPTION OF RESULTS

In general, the severity of the reactions observed in these experiments was less than that observed in the previously described interstitial

experiments. Also, the differences in reaction between the radium and the cobalt 60 were significantly less, and the radium reaction was identical to the cobalt 60 reaction in a greater number of rabbits (Fig. 2).

Temporal Relationships of the Radiation Reactions. These are indicated in Table I. The cobalt reaction appeared about one day sooner on the average, whereas the reactions were maximal on the two sides about the same time (21 days). The average healing time was four weeks on both sides.

The initial reaction observed was usually a slight erythema with occasionally a very minimal induration in an area measuring approximately 2.5 by 2.5 cm. in diameter. Occasionally, after a long latent period in which no reaction was seen, a rather severe reaction seemed to appear in a matter of two or three days.

Proliferation and rapid regrowth of the hair on either side was a frequent early manifestation; but soon epilation supervened, leaving an erythematous and sometimes moist denuded area.

The reaction times and curves were identical in 33 of the 58 rabbits; the cobalt reaction seemed to move along faster than the radium reaction in 12 of the rabbits; whereas the radium reaction moved faster than the cobalt reaction in 13 of the rabbits.

Comparison of the Severity of the Two Reactions. The ultimate severity of the two reactions attained by the radium and the cobalt 60 treated areas was considered the same in 30 of the 58 rabbits in the two "gross" series of experiments. In no instance in this series was a severe necrosis obtained, such as we saw in our interstitial experiments.[5] The maximal reaction was usually a moist reaction which persisted for approximately two weeks. Complete healing was obtained, on the average, in four weeks with both the cobalt and the radium.

The over-all healing time varied between three and nine weeks in the entire series of animals.

The cobalt reaction was considered to be slightly more severe than the radium reaction in 20 of the rabbits, and moderately more severe in 7 of the rabbits. Slightly greater severity was considered when the induration of the area or the intensity of the redness was slightly greater on one side than on the other.

The radium reaction was moderately more severe than the cobalt reaction in only 1 of the rabbits (in Series 1).

Character of the Scars Obtained from the Two Modalities of Radiation. The scars obtained on the two sides were usually identical. They were usually pale, thin scars, quite pliable, measuring approximately 2.5 cm. in diameter. Occasionally there were telangiectasias noted. In 2 instances, the radium scar was slightly thicker

TABLE I

COMPARISON OF RESULTS: COBALT 60 VS. RADIUM IN IDENTICAL DOSES WHEN THE COBALT 60 IS ENCASED IN HYPERCHROME STEEL 0.23 MM. WALL THICKNESS, ACTIVE LENGTH 2.0 CM. IN SERIES II; AND WHEN COBALT 60 IS ENCASED IN 0.5 MM. GOLD, ACTIVE LENGTH 1.6 CM. IN SERIES I. DOSE: 7,000 R; TIME: 144 TO 150 HOURS; AREA: 2 BY 2 CM.; PATERSON-PARKER DISTRIBUTION

	Series I (30 Rabbits)			Series II (28 Rabbits)			Total: 58 Rabbits		
	Radium	Cobalt 60	Same	Radium	Cobalt 60	Same	Radium	Cobalt 60	Same
Average time for reaction to appear	13 days	11.7 days		9.3 days	8.4 days		11 days	10 days	
Average time for maximal reaction	21.2 days	19.8 days		21 days	21 days		21 days	20.5 days	
Average healing time	4 weeks (21–63 days)	4 weeks (22–63 days)		29 days	29 days		4 weeks	4 weeks	
Which reaction more severe	1	8 slight 2 mod.	19	0	12 slight 5 mod.	11	1	27	30
Which reaction faster	11	2	17	2	10	16	13	12	33
Which scar thicker	1	0	29	1	5	22	2	5	51
	Radium	Cobalt 60	Both	Radium	Cobalt 60	Both	Radium	Cobalt 60	Both
No. rabbits having secondary breakdown	1	1	2	1	2	0	2	3	2
Healing time	3 weeks	3½ weeks		2 to 3 wk.	2 to 3 wk.		3 weeks	3 weeks	
Average time when secondary breakdown appeared	46 days	46 days		60 days	69½ days		53 days	58 days	

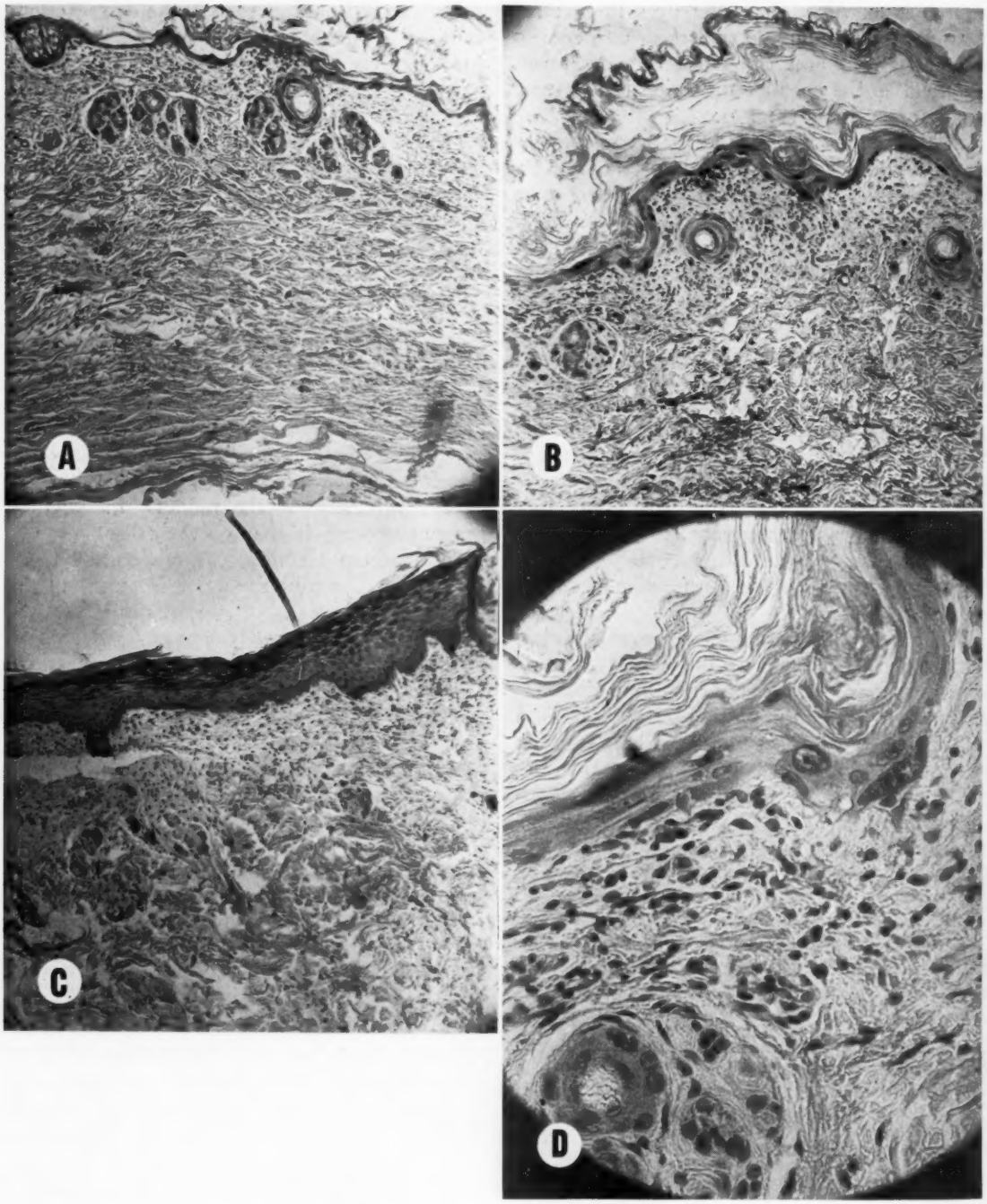
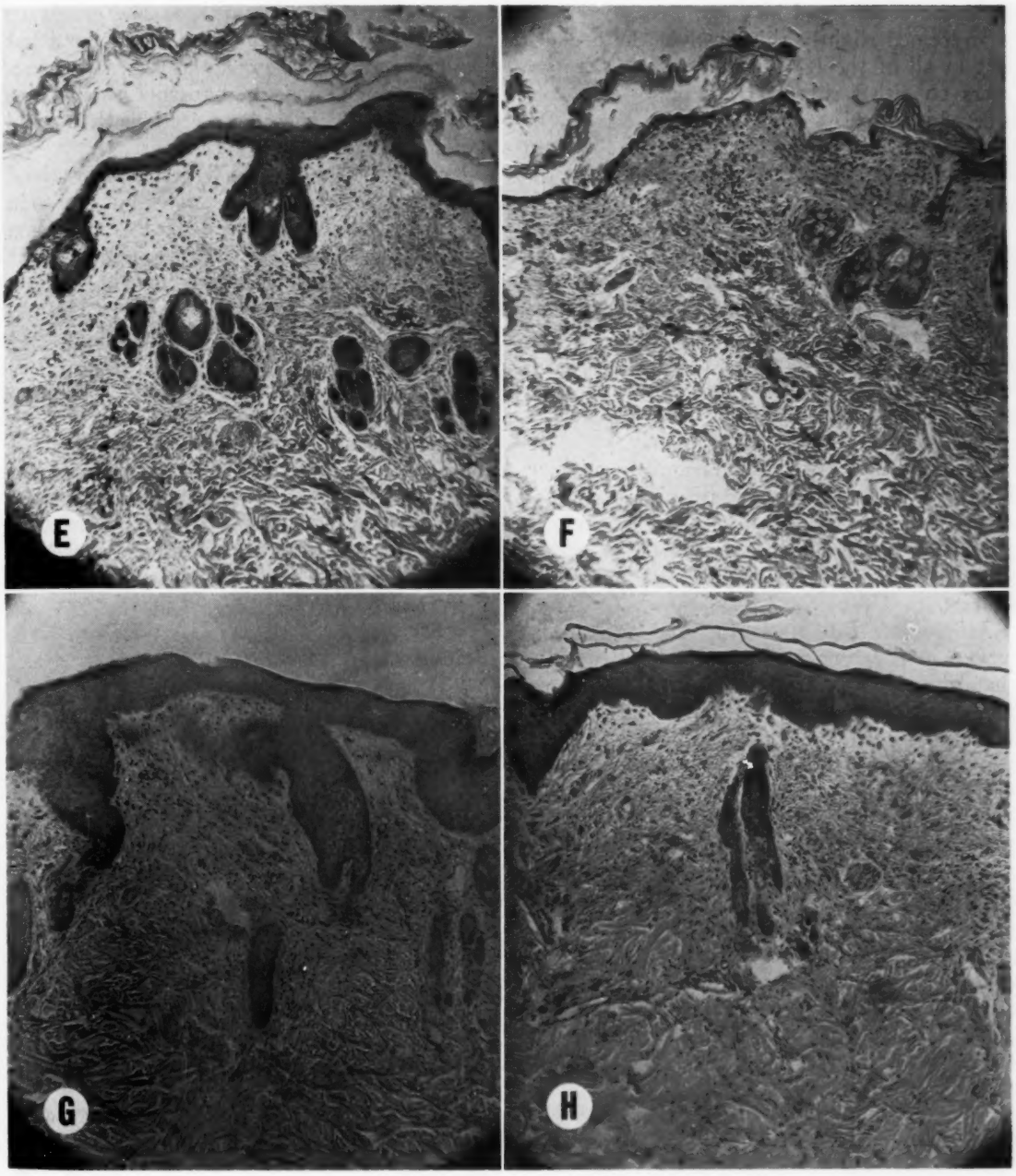


FIG. 3. Photomicrographic studies of the rabbits' skin following the external application of identical doses of cobalt 60 and radium (7,000 r calculated to a layer of skin 0.25 cm. beneath the surface). Plaques and all factors were identical. (*A*) Radium reaction at eight days. (*B*) Cobalt reaction in same rabbit at eight days (Rabbit No. 71). (*C*) High power view of (*B*). (*D*) Radium reaction at fourteen days (Rabbit No. 69). (*E*) (*F*) Cobalt reaction in same rabbit at fourteen days in two different areas, one demonstrating ulcera-



tion (*F*) and the other hyperplasia of epithelial elements (*E*) (Rabbit No. 69). (*G*) Radium reaction at twenty-one days. (*H*) Cobalt reaction in same rabbit at twenty-one days. The hyperplasia in the cobalt reaction tends to be somewhat less marked at this time.

It is noted that the hyperplasia of the epithelial component is perhaps slightly greater early in the cobalt reaction series, and disappears rather quickly, giving rise to what appears to be somewhat greater destruction, greater ulceration, and greater infiltration in the dermis.

than the cobalt, and in 5 instances the cobalt scar seemed slightly thicker than the radium; but in all of the rest of the animals (51) the scars on either side of the animal were considered identical.

Secondary Breakdown. In 7 of the rabbits secondary breakdown of the irradiated areas occurred: In 2 of these both sides broke down virtually simultaneously, and followed similar courses thereafter, healing in sixty-nine to ninety days. In 2 rabbits the cobalt reaction broke down and the radium reaction did not; and in 3 rabbits the reverse was obtained. The differences in secondary breakdown are therefore insignificant in this series in contrast to the previous experiments where the steel-encased cobalt 60 was employed interstitially.

Healing Time. The time for complete primary healing of the two radiation reactions was considered identical in most of the rabbits despite the fact that the height of the cobalt reaction was slightly greater in almost one-half of the rabbits.

Microscopic Findings. The reactions as observed in different rabbits would differ more than the two reactions observed in the same animal, when comparing the cobalt 60 reactions with those produced by the radium. Also, the reactions observed in this series of experiments did not approach in severity those observed following interstitial implantation.

At the end of one week there was usually a considerable hyperplasia of all of the epithelial elements, with the greatest hyperplasia in the stratum germinativum. There was also a hyperplasia of the granular layer. The dermis was moderately edematous, with a tendency for infiltration of leukocytes. There were occasional areas of ulceration, with evidence of polymorphonuclear infiltration in the dermis beneath. The basal cells tended to be larger and more pleomorphic than normal, with some evidence of mitoses. The hair follicles also appeared hyperplastic. In general, the hyperplastic and exudative response was slightly more pronounced in the cobalt 60 sections than in the radium sections from the same animal (Fig. 3).

By the end of the second week there was usually considerable ulceration in the cobalt 60 sections, marked exudation of inflammatory cells in the dermis, very extensive edema, and very little residual hyperplasia of the epithelial elements. Indeed, this period was characterized largely by the inflammation and ulceration, in contrast to the first week which was characterized by hyperplastic response. The cobalt 60 sections tended to be more ulcerative and less hyperplastic than the comparable radium sections. At this period, the hyperplasia tended to persist more in the radium sections than could be found in the cobalt 60 sections.

By the third week the hyperplasia was still very great in the radium sections, but less so in the cobalt 60 sections. There was less ulceration and less inflammation than was apparent at the two week period. The epithelium showed evidence of reappearance in the cobalt 60 sections but the cells were pyknotic and small, and the various epithelial layers thin.

In general, the impression was gained from these microscopic studies that there was an earlier hyperplasia in the cobalt 60 treated areas, with more extensive inflammation and ulceration, but healing time seemed about the same on both sides. *The degree of hyperplasia seemed greater in the radium areas, and the radium treated areas did not seem to ulcerate quite as extensively.*

DISCUSSION

It was our conclusion that although the differences between the cobalt and radium reactions were not great in these experiments, nevertheless there was a decided tendency for the cobalt reaction to be somewhat greater in slightly less than half of the experimental animals.

In view of the differences noted between the cobalt 60 irradiated areas of rabbit skin and the radium irradiated areas previously described in the interstitial experiments, it was our intention in the present series of experiments to try to evaluate what factor or factors might be operating which might explain these slight differences.

In previous interstitial experiments certain variables were noted and no effort was made to control them. It was our desire at that time to compare the cobalt 60 radiation as we intended to use it as against the radium radiation methods with which we were familiar. In that respect the previous interstitial experiments differed from the present. At the present time every effort was made to control every variable.

The variables which were still to be controlled were:

(1) Quantity of radiation as measured in gamma roentgens;
(2) Modality by which the radiation is delivered;
(3) The distance "*h*" of irradiation;
(4) The area and tissue irradiated and its shape;
(5) The time of irradiation (time factor).

Quantity of Radiation as Measured in Gamma Roentgens. Seven thousand gamma roentgens as calculated to a layer 0.25 cm. beneath the skin were employed. This was a constant which was readily controlled since the plaques were carefully constructed in identical fashion, and since the plaques were composed of a rigid medium (masonite presdwood). It was considered advisable to calculate this dosage to a point 0.25 cm. beneath the rabbit skin since it became evident that to obtain an observable and comparable reaction in less than seven days it would be necessary to increase the surface dose to this extent. Since the average density of masonite presdwood and the average density of the skin approach one another, these are biologically equivalent materials, and hence the dosage can be considered identical in both instances.

The contribution from the radium side to the cobalt 60 side of the animal was calculated to be negligible.

Modality by Which the Radiation Is Delivered. In all 71 animals, the radiation was delivered in identical fashion on the two sides of the animal. All factors were identical in 43 of the rabbits (of which number 13 rabbits are in the microscopic series), with the exception that cobalt 60 was used on the left side of the animal and radium emanation on the right. In the other 28 animals, one additional variable was introduced—namely, the original hyperchrome steel-encased cobalt 60 needles were employed in lieu of the gold-encased cobalt 60 needles. Since the results are very similar in the two series of experiments, it is considered that the differences in construction of the cobalt 60 needles are not significant. It would appear that there is no significant difference observed between the plaques of cobalt 60 made of hyperchrome steel-encased cobalt 60 needles, and gold-encased cobalt 60 needles, when all other factors are controlled.

Distance "h" of Irradiation. The distance "*h*" to the skin was 0.25 cm. on both sides, and hence identical.

Area Irradiated. The areas irradiated in both instances were identical for both the cobalt 60 and radium. Two by two centimeters was the area employed throughout this entire series of experiments on both sides. Since the radiation was administered by means of plaques, the area of irradiation could be controlled with extreme accuracy.

Type of Tissue Irradiated. Identical areas of the skin of the rabbit were irradiated by both the cobalt 60 and the radium since the same animal was employed in the two series of experiments in every case, and since symmetrical sides of the animal were employed for the radium and cobalt treated areas. No investigation has been made with other tissues than the rabbit skin.

Time Factor. In order to overcome the slight differences in the intensities of the two types of needles, an intermittent application had to be employed for the radium where the comparable intensity was somewhat greater. Since the fractionation, however, was minimal, and since the dose rates were very similar, and since the over-all time of radiation was kept constant in this series of experiments, we can consider that the time factor was kept constant in this series of experiments. The over-all radiation time for both modalities was in the order of five days in this series of experiments for delivery of the 7,000 gamma roentgens as indicated.

It is also notable that the reaction rates of the two modalities in all 58 rabbits (of the gross study) were not significantly different, but the cobalt reaction was considered slightly or moderately more severe in 27 (47 per cent); the two reactions were the same in 30 (52 per cent); and in only 1 rabbit was the radium reaction regarded as more severe. The time factor, if in favor

of any one reaction, would have been in favor of producing a slightly more severe radium reaction, since the dose intensity was slightly greater for the radium than the cobalt. Since the reverse was obtained we feel certain that the time factor was not a significant variable in this series of experiments.

Superimposed Infection or Trauma. We were unable to observe any significant superimposed infection or evidence of trauma in this series of animals. It is possible that the secondary breakdown observed might be related to the superimposed infection or trauma. In either instance, this was not significantly different between the radium and the cobalt and hence need not be considered as a significant factor in this series of experiments.

Animal or Individual Differences. There is no doubt that there are differences from one species to another so that a direct parallelism between rabbit skin and human skin is not possible. This series of experiments will have to be repeated with human skin. Unfortunately, the intensities of the reactions to be obtained on human skin experiments will not reach the heights to which we were able to subject these rabbits' skins. Nevertheless, a faint erythema should be obtainable and hence the speed of the reaction and the intensity of the reaction still will be comparable to some extent. These experiments are in the process of being performed at the present time, and preliminary evaluation of results with 3,000 r would corroborate our animal experiments.

Quality of Cobalt 60 Radiation as Compared with Radium. Although it would appear from these experiments that the rabbit skin effects are slightly more severe from cobalt 60 than from radium, when identical calculated doses are employed, the conclusion is still not warranted that these differences are a measure of the quality differences of the radiation. Indeed, it is difficult to believe in the light of other evidence that such is the case.

It should be recalled that these are *calculated* doses in which the dose for cobalt 60 was obtained by the simple conversion of Paterson-Parker tables constructed for radium, by a single factor (0.619 now considered to be the most accurate factor). These tables admittedly do not take into account the factors of oblique filtration and self-absorption, and admittedly provide a homogeneous radiation only within ± 10 per cent for the most part. Suffice it to say, however, that the above described experiments are actually a measure of the clinical applicability of the newly constructed tables (based upon simple conversion of Paterson-Parker values) as well as a comparison of the quality effects of cobalt 60 as against radium.

Additional Mathematical Considerations. Our tables for the utilization of cobalt 60 are being reported in detail elsewhere.[6]

As a test of the mathematical applicability of the simple conversion factor 0.619, we compared our table for dosage delivery from a 2 cm. hyperchrome steel-encased cobalt 60 needle with a similarly calculated table for a 2 cm., 0.5 mm. platinum-encased radium needle provided by Dr. Edith H. Quimby—multiplying the radium values by 0.619. This comparison is presented in Table II. It is obvious from a study of this table that at the closer ranges (of greatest interest to us here) differences of $+6.4$ per cent to -24.3 per cent are noted. Beyond 1.5 cm. "h" the differences become negligible.

As a second test of the mathematical applicability of the Paterson-Parker distribution rules to the problem at hand, the following calculations were made:[6]

Utilizing Quimby's values for roentgens delivered by linear sources of radium, it is possible to calculate the roentgens delivered at various points in a plane 0.5 cm. from the radiating plane. Similarly, by utilizing our own tables for roentgens delivered per millicurie hour at various points around linear sources of cobalt 60, it is possible to calculate the roentgens delivered at various points in a plane 0.5 cm. from the radiating plane.

TABLE II

COMPARISON OF THE GAMMA ROENTGENS PER MILLICURIE HOUR OF COBALT 60 AS CALCULATED BY TAKING INTO ACCOUNT DISTANCE, OBLIQUE FILTRATION, AND SELF-ABSORPTION AS AGAINST BY TAKING THE QUIMBY VALUES AND CONVERTING BY THE SIMPLE FACTOR 1.356*/0.84

(2.0 cm. enclosed cobalt 60 wire: wire diameter 1.0 mm.; wall thickness 0.23 mm.; bore diameter 1.19 mm.; over-all diameter 1.65 mm.)

Cm. from Tube		Distance Along Tube Axis: Cm. from Center								
		0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
0.5	Our determined values	28.23	26.10	16.74	7.13	3.56	2.10	1.36	0.94	0.70
	Quimby converted values	29.05	27.76	14.69	6.21	3.15	1.86	1.23	0.79	0.53
	Percentage difference	+2.9%	+6.4%	−6.3%	−12.9%	−11.5%	−11.4%	−9.6%	−15.9%	−24.3%
1.0	Our determined values	10.11	9.41	7.08	4.60	2.91	1.93	1.33	0.98	0.74
	Quimby converted values	10.09	9.20	7.02	4.36	2.71	1.77	1.21	0.89	0.68
	Percentage difference	−0.2%	−2.2%	−0.8%	−5.2%	−6.9%	−8.3%	−9.0%	−9.2%	−8.1%
1.5	Our determined values	5.13	4.78	3.99	3.05	2.20	1.63	1.19	0.88	0.71
	Quimby converted values	5.37	4.89	4.15	3.05	2.18	1.57	1.13	0.87	0.69
	Percentage difference	+4.6%	+2.3%	+4.0%	0.00%	−0.9%	−3.7%	−5.0%	−1.1%	−2.8%
2.0	Our determined values	3.01	2.90	2.54	2.12	1.67	1.31	1.03	0.80	0.66
	Quimby converted values	3.16	2.99	2.57	2.11	1.65	1.26	0.98	0.77	0.63
2.5	Our determined values	1.98	1.92	1.75	1.52	1.28	1.06	0.87	0.71	0.58
	Quimby converted values	2.02	1.95	1.79	1.55	1.29	1.05	0.84	0.69	0.56
3.0	Our determined values	1.40	1.36	1.27	1.25	1.00	0.85	0.72	0.61	0.52
	Quimby converted values	1.44	1.42	1.31	1.16	1.00	0.84	0.71	0.60	0.50
3.5	Our determined values	1.03	1.02	0.96	0.89	0.79	0.71	0.61	0.53	0.46
4.0	Our determined values	0.80	0.79	0.75	0.71	0.65	0.58	0.52	0.46	0.41
	Quimby converted values	0.82	0.81	0.77	0.73	0.65	0.58	0.52	0.45	0.40
4.5	Our determined values	0.64	0.63	0.60	0.57	0.53	0.49	0.45	0.40	0.35
5.0	Our determined values	0.51	0.50	0.49	0.47	0.45	0.42	0.37	0.34	0.31
	Quimby converted values	0.53	0.53	0.52	0.48	0.45	0.42	0.39	0.35	0.32

* The original Quimby values referred to a 2 cm. length (active length) radium needle filtered by 0.5 mm. platinum. Quimby estimated the maximum error at 10 per cent from omission of consideration of self-absorption.

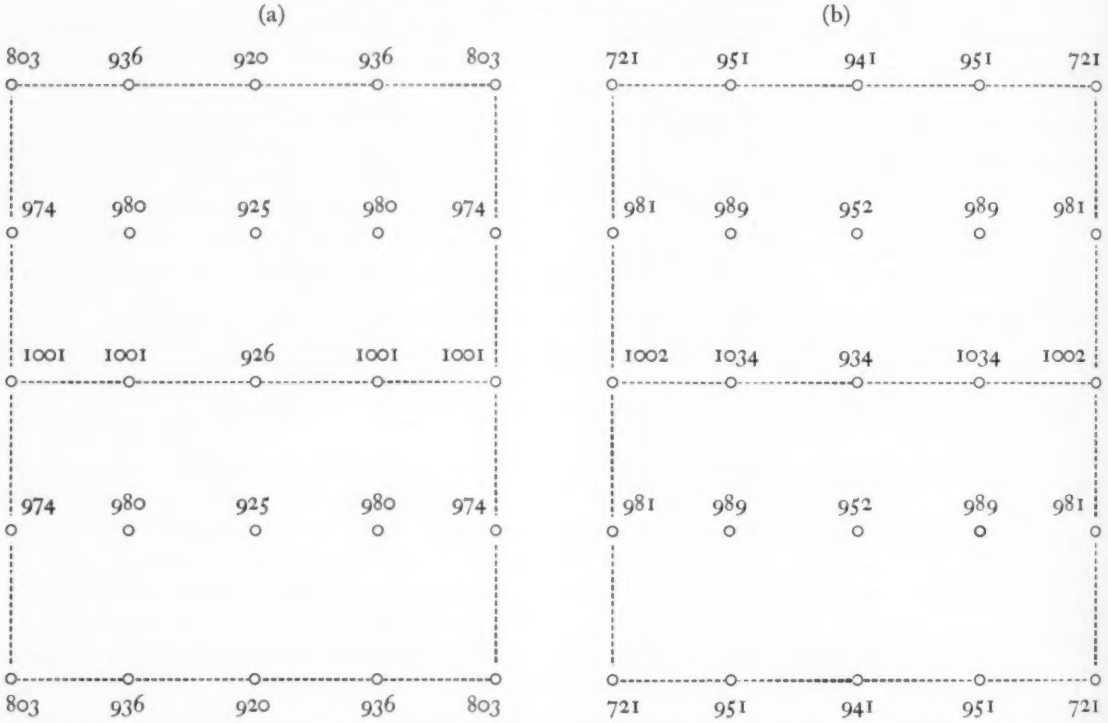
Adopting 1,000 roentgens as the desired dose to be delivered, and utilizing Paterson-Parker values to give us the milligram hours necessary for radium, and the Paterson-Parker value ×0.619 as the millicurie hours necessary for cobalt 60, and utilizing Paterson-Parker distribution rules, the values shown in Table III (a) and (b) demonstrate the calculated dosage delivered to these identical planes with these two modalities of radiation. The differences, for the most part, are minor with the exception of the four corners (721 r for radium, as against 803 r for cobalt). It is of significance that these mathematical differences do exist, and may help explain the differences observed in our experiments.

The results of these experiments and calculations are important, however, in indicating that it is probable that the utilization of these cobalt 60 tables is reasonably accurate. In 52 per cent of the rabbits, identical reactions were observed, and in a biological experiment of this type such agreement is good; and of the remainder, the differences were slight in 35 per cent, moderate in 12 per cent. To be ultraconservative, an additional correction factor (of perhaps 15 per cent) may be applied to obtain comparable effects from the cobalt 60 and radium. It is probable, however, that in clinical applications 7,000 r in five to seven days could be administered with safety in accordance with established Paterson-Parker techniques. At present we prefer to use 6,000 to 6,500 r with cobalt

TABLE III

COMPARISON OF DOSAGE AT VARIOUS POINTS IN A PLANE 0.5 CM. FROM THE PLANE OF RADIATING SOURCES (1,000 GAMMA ROENTGENS—PATERSON-PARKER); AREA 2 BY 2 CM.

(a) Under cobalt 60 plaque with hyperchrome steel needles; and
(b) Under radium plaque, with radium encased in 0.5 mm. platinum* (0.5 cm. intervals)



* Quimby tables were used to calculate the roentgen delivery to these points from the radium sources; and our own tables were used for the cobalt 60.

60 in situations where previously we had used 7,000 r with radium.

SUMMARY AND CONCLUSIONS

A total of 71 rabbits was studied, 58 from the standpoint of comparison of the gross radiation effects of identical externally applied radium and cobalt 60 plaques, and 13 from a microscopic standpoint at one, two, three, and four week intervals.

In 30 rabbits of the gross series, and all 13 of the microscopic series, an effort was made to apply identical gamma roentgen doses of both the radium and the cobalt 60 to identical areas of abdominal skin of the rabbit. A calculated dosage of 7,000 gamma roentgens was delivered to a layer 0.25 cm. beneath the skin surface. All of the variables were controlled and indeed the only significant variable remaining was the use of cobalt 60 as against the gamma rays obtained from the disintegration products of radium 226.

The method of calculation was by simple conversion of Paterson-Parker tables by a factor: 0.84/1.356.

In 28 rabbits the original hyperchrome steel-encased cobalt 60 needle was employed, but all other factors were the same. The results were similar in both series, suggesting that the difference in needle construction was not a significant factor.

Identical reactions were obtained in every respect in 30 of the 58 rabbits of the gross series. In 27 rabbits the cobalt 60 reaction was slightly or moderately more severe; and in only one rabbit was the radium reaction more severe.

In 12 of the rabbits the cobalt 60 reaction appeared to arise somewhat more quickly and reach its maximum more quickly than did the radium reaction. The radium reaction progressed more quickly in 13 rabbits. In 33 rabbits the reaction rate was the same. This, therefore, is not a significant difference.

The differences observed were, for the most part, not very great, and probably could be tolerated in the clinical application of cobalt 60. We are finding it desirable, however, in employing Paterson-Parker converted tables, to utilize 6,000 r to 6,500 r in treatment with cobalt 60 in five to seven days, where 7,000 r would be used with radium in interstitial and intracavitary or plaque techniques.

In the microscopic studies, *slight* differences were also noted pointing toward an earlier hyperplastic and greater ulcerative reaction on the cobalt side.

One cannot conclude that the differences observed were necessarily a comparison of qualities of radiation from cobalt 60 and radium. These experiments compared these two different qualities of radiation by *calculated* doses (based on Paterson-Parker techniques and small areas). These experiments are just as much a test of this method of calculation of dose of cobalt 60 applications, as a comparison of radiation effects from these two different modalities of radiation.

It will be highly desirable to check these calculated values by experimental determination of isodose curves for further study of the differences noted in these experiments.*

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* For discussion see page 330.

DOSAGE TABLES FOR COBALT 60 FOR USE WITH INTERSTITIAL, PLAQUE, AND INTRACAVITARY APPLICATIONS*†

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IN THE course of many years of radium and radon application, a wealth of physical data has been accumulated. Such physical data are essential in clinical applications. Similar data must be provided for use with cobalt 60.

Presentation of Paterson-Parker Converted Tables. Paterson-Parker tables[2] and rules for radium distribution have proved of great value in radium usage. On the basis that cobalt 60 delivers 1.356 roentgens per hour at 1 meter (rhm) (calculated value), and that radium (0.5 mm. platinum-encased) delivers 0.84 rhm, Paterson-Parker tables for 0.5 mm. platinum-encased radium may be multiplied by the ratio 0.84/1.356, or 0.619, and "Paterson-Parker-like" cobalt 60 tables may thus be obtained.[5]

Such tables are herein presented (Table I) with the realization that a slight modification of these tables may be necessary when isodose patterns are established for cobalt 60 by physical measurement. From our present "mean dose" calculations at 0.5 cm. "*h*" for both radium and cobalt 60 for areas 2 by 2 cm., 2 by 4 cm., and 4 by 6 cm., it would seem that accuracy within 10 to 15 per cent per field is achieved except at the four corners of the field (when compared with similar calculations for radium) but homogeneity is obtained in general when Paterson-Parker distribution rules are followed (Tables II, III, and IV).

Dosage Delivered around Linear Sources. Upon the advice of Dr. Edith H. Quimby, we have also constructed tables whereby it is possible to obtain the roentgens delivered per millicurie hour at any point around various linear sources of cobalt 60 (encased in 16 gauge hyperchrome steel tubing) from 1 cm. to 6 cm. in length (Tables V, VI, VII, VIII, IX, and X). These calculations were made by applying the summated oblique thicknesses of the cobalt and steel to a copper absorption curve for estimating correction for oblique filtration and self-absorption.

The absorption curves of cobalt 60 in various substances are shown in Figure 1, and it is readily apparent that the absorption curves for copper and steel are almost identical and the error introduced is negligible, particularly for small thicknesses of material.

Tables (Tables XI and XII) are also presented for 1 cm. linear sources which are 4 mm. in diameter and encased in 2 mm. brass; and similar sources with the additional application of 5 by 4 mm. lead cylinders at either end for additional filtration. We have utilized these latter sources in the colpostat portion of the Ernst type applicator for additional protection to rectum and bladder.

Possible Additional Correction Factors may be necessary as indicated by biological comparisons of skin reactions obtained in rabbits and on human skin, with identical doses of radium and cobalt 60—but these experiments are being reported separately.[3,4,5]

SUMMARY

Dosage tables for cobalt 60 utilization are presented. These tables permit the utilization of cobalt 60 in Paterson-Parker

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TABLE I

MILLICURIE HOURS PER 1,000 GAMMA ROENTGENS FOR DIFFERENT AREAS AND VARIOUS TREATING DISTANCES; COBALT 60 WIRE ENCASED IN HYPERCHROME STEEL, WALL THICKNESS 0.23 MM. OR LESS

Area Cm.²	Treating Distance in cm. (h)									
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
0	18.57	73.66	165.89	294.64	460.54	662.95	902.50	1178.58	1493.03	1842.14
1	42.09	105.85								
2	60.04	131.85	232.12	370.16	535.43	740.94	987.30	1264.62	1575.35	1929.42
3	74.28	152.89								
4	87.28	172.08	285.98	432.06	600.43	807.79	1060.35	1341.99	1649.63	2007.42
5	99.66	189.41								
6	109.56	206.13	331.78	484.06	659.85	869.69	1127.82	1415.03	1719.58	2079.84
7	118.85	222.22								
8	127.51	237.70	370.78	529.24	714.94	928.50	1190.96	1482.50	1784.58	2149.17
9	136.80	252.55								
10	145.46	268.03	405.44	571.34	764.46	984.21	1250.38	1547.50	1848.95	2216.02
11	153.51	282.26								
12	161.56	297.12	439.49	612.81	812.13	1035.59	1307.33	1611.26	1910.85	2279.16
13	169.61	310.74								
14	178.27	324.36	472.92	651.81	857.93	1085.11	1361.80	1670.06	1971.51	2342.91
15	186.94	337.97								
16	194.98	350.35	503.87	688.95	903.74	1132.77	1413.18	1727.01	2030.32	2403.58
17	203.03	362.11								
18	211.70	374.49	534.20	724.23	943.97	1179.19	1462.70	1782.10	2086.03	2466.71
19	219.74	385.64								
20	227.79	396.78	563.29	758.27	982.97	1225.00	1513.45	1835.33	2142.36	2525.52
22	243.27	417.21	594.24	792.32	1021.35	1268.33	1561.12	1886.09	2197.45	2583.71
24	258.12	437.63	623.95	826.36	1059.73	1310.42	1608.16	1934.99	2252.54	2641.27
26	273.60	456.20	653.66	859.17	1094.39	1354.37	1652.73	1980.80	2305.16	2696.36
28	288.45	474.77	680.90	890.12	1130.29	1395.23	1697.30	2027.22	2354.68	2752.07
30	303.31	492.10	706.90	920.45	1163.72	1436.08	1743.72	2072.41	2403.58	2806.55
32	317.55	509.44	733.51	951.40	1198.38	1473.22	1787.67	2116.98	2454.95	2859.78
34	332.40	528.63	758.89	982.35	1233.05	1511.60	1829.76	2160.31	2505.09	2909.30
36	345.40	544.10	784.89	1013.92	1267.71	1548.74	1870.62	2203.02	2553.37	2960.68
38	359.64	562.67	809.65	1043.01	1299.90	1585.88	1911.47	2245.11	2598.56	3010.19
40	373.26	578.15	833.17	1072.11	1332.09	1621.78	1949.85	2287.20	2644.99	3059.10
42	386.26	595.48	856.70	1101.82	1363.66	1657.06	1990.08	2328.68	2691.41	3107.38
44	398.64	612.81	878.98	1129.67	1395.84	1691.73	2027.22	2368.29	2737.84	3154.42
46	411.63	628.28	901.88	1157.53	1426.79	1725.77	2064.36	2407.91	2781.79	3202.71
48	424.01	645.62	922.31	1185.38	1457.13	1759.82	2101.50	2447.53	2825.73	3249.75
50	436.39	663.57	942.12	1212.00	1486.84	1793.24	2138.64	2487.14	2867.83	3297.41
52	448.77	679.66	961.93	1240.48	1516.55	1826.05	2174.55	2525.52	2910.54	3342.60
54	460.54	696.37	982.97	1267.09	1547.50	1858.86	2209.21	2563.90	2951.39	3389.02
56	471.68	713.09	1001.54	1294.95	1577.21	1891.04	2243.87	2602.89	2992.86	3434.21
58	483.44	728.56	1021.35	1322.80	1607.54	1922.61	2276.68	2641.27	3034.96	3478.78
60	495.20	746.51	1041.16	1349.42	1637.87	1956.04	2311.96	2679.03	3076.43	3522.11
62	506.34	761.37	1059.73	1375.42	1666.35	1988.23	2346.01	2716.79	3117.90	3565.44
64	518.10	779.94	1077.06	1400.18	1693.58	2019.18	2380.05	2752.69	3159.99	3608.77
66	529.24	795.41	1095.01	1424.94	1722.06	2048.89	2414.10	2788.59	3200.85	3652.10
68	540.39	812.75	1112.96	1449.70	1750.53	2079.84	2445.05	2823.88	3238.61	3693.57
70	550.91	829.46	1130.91	1473.22	1779.62	2110.79	2476.62	2858.54	3276.99	3734.43
72	562.05	846.17	1149.48	1497.98	1808.72	2141.74	2508.81	2893.82	3314.74	3774.66
74	573.81	862.89	1168.05	1519.64	1837.19	2172.69	2540.99	2929.73	3353.12	3814.28
76	584.95	879.60	1185.38	1541.31	1865.05	2203.64	2573.80	2965.63	3392.12	3853.27
78	596.10	895.07	1201.48	1564.21	1892.90	2233.35	2605.99	2999.67	3430.50	3892.27

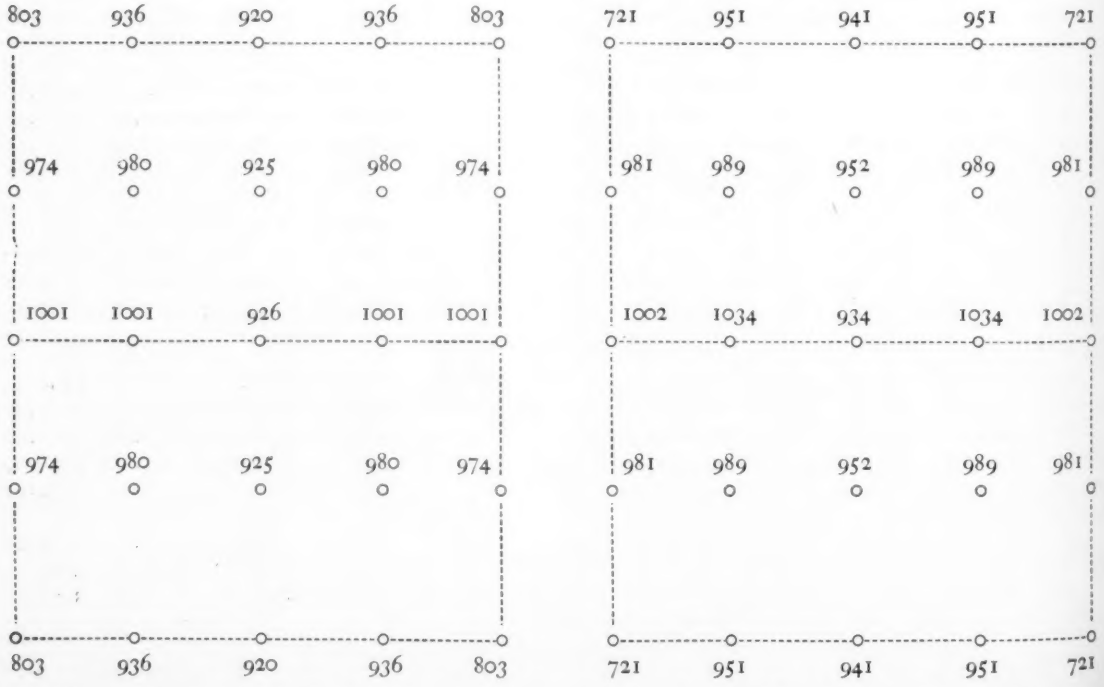
TABLE I (*Continued*)

Area Cm.²	Treating Distance in cm. (h)									
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
80	607.24	911.79	1216.95	1585.88	1920.76	2263.68	2636.94	3033.10	3466.40	3930.65
84	628.90	943.36	1250.38	1627.97	1975.85	2324.34	2698.84	3103.67	3540.68	4006.79
88	651.19	973.07	1284.42	1670.06	2031.56	2382.53	2761.98	3172.99	3613.72	4084.16
92	672.85	1002.78	1318.47	1711.53	2086.65	2440.72	2822.64	3240.46	3685.53	4159.68
96	694.52	1032.49	1353.13	1750.53	2141.12	2496.43	2882.68	3305.46	3756.09	4235.20
100	714.94	1062.20	1385.32	1788.91	2194.35	2550.28	2940.25	3370.45	3825.42	4305.76
120	809.03	1213.24	1553.69	1968.42						
140	905.60	1358.09	1725.77	2147.93						
160	995.35	1493.03	1891.04	2312.58						
180	1080.77	1619.92	2050.13	2482.19						
200	1163.72	1745.58	2203.64	2654.27						
220	1242.95	1861.95	2355.29	2818.93						
240	1319.71	1980.80	2503.85	2986.06						
260	1396.46	2094.08	2654.27	3153.80						
280	1468.27	2203.64	2804.07	3317.84						
300	1544.40	2319.39	2946.44	3484.97						
320	1623.02	2428.96	3085.10	3647.15						
340	1694.20	2540.99	3218.80	3803.75						
360	1766.01	2649.32	3359.31	3954.17						
380	1837.19	2757.64	3484.97	4099.64						
400	1906.52	2859.78	3614.96	4248.82						

TABLE II

COMPARISON OF DOSAGE AT VARIOUS POINTS IN A PLANE 0.5 CM. FROM THE PLANE OF RADIATING SOURCES (1,000 GAMMA ROENTGENS—PATERSON-PARKER); AREA 2 BY 2 CM. (0.5 CM. INTERVALS)

(a) Under cobalt 60 plaque with hyperchrome steel needles; and
(b) Under radium plaque, with radium encased in 0.5 mm. platinum*



* Quimby tables were used to calculate the roentgen delivery to these points from the radium sources; and our own tables were used for the cobalt 60.

Table III

COMPARISON OF DOSAGE AT VARIOUS POINTS AT 5 MM. INTERVALS IN A PLANE 0.5 CM. FROM THE PLANE OF RADIATING SOURCES (1,000 GAMMA ROENTGENS—PATERSON-PARKER); AREA 2 BY 4 CM.

(a) Under cobalt 60 plaque with hyperchrome steel needles; and
(b) Under radium plaque, with radium encased in 0.5 mm. platinum*

(a)

817	926	935	945	941	945	935	926	817
956	922	871	835	824	835	871	922	956
1009	986	902	902	887	902	902	986	1009
956	922	871	835	824	835	871	922	956
817	926	935	945	941	945	935	926	817

(b)

740	952	955	959	990	959	955	952	740
972	900	915	926	943	926	915	900	972
1003	1029	922	900	921	900	922	1029	1003
972	900	915	926	943	926	915	900	972
740	952	955	959	990	959	955	952	740

* Quimby tables were used to calculate the roentgen delivery to these points from the radium sources; and our own tables were used for the cobalt 60.

TABLE IV

COMPARISON OF DOSAGE AT VARIOUS POINTS IN A PLANE 0.5 CM. FROM THE PLANE OF RADIATING SOURCES (1,000 GAMMA ROENTGENS—PATERSON-PARKER); AREA 4 BY 6 CM. (0.5 MM. INTERVALS)

(a) Under cobalt 60 plaque with hyperchrome steel needles; and
(b) Under radium plaque with radium encased in 0.5 mm. platinum*

(a)

775	881	894	905	912	913	916	913	912	905	894	881	775
927	925	911	899	909	905	907	905	909	899	911	925	927
1009	1008	950	940	910	943	946	943	910	940	950	1008	1009
1015	961	929	911	913	907	911	907	913	911	929	961	1015
1041	1009	971	901	922	951	953	951	922	901	971	1009	1041
1015	961	929	911	913	907	911	907	913	911	929	961	1015
1009	1008	950	940	910	943	946	943	910	940	950	1008	1009
927	925	911	899	909	905	907	905	909	899	911	925	927
775	881	894	905	912	913	916	913	912	905	894	881	775

* Quimby tables were used to calculate the roentgen delivery to these points from the radium sources; and our own tables were used for the cobalt 60.

Table IV (*Continued*)

(b)

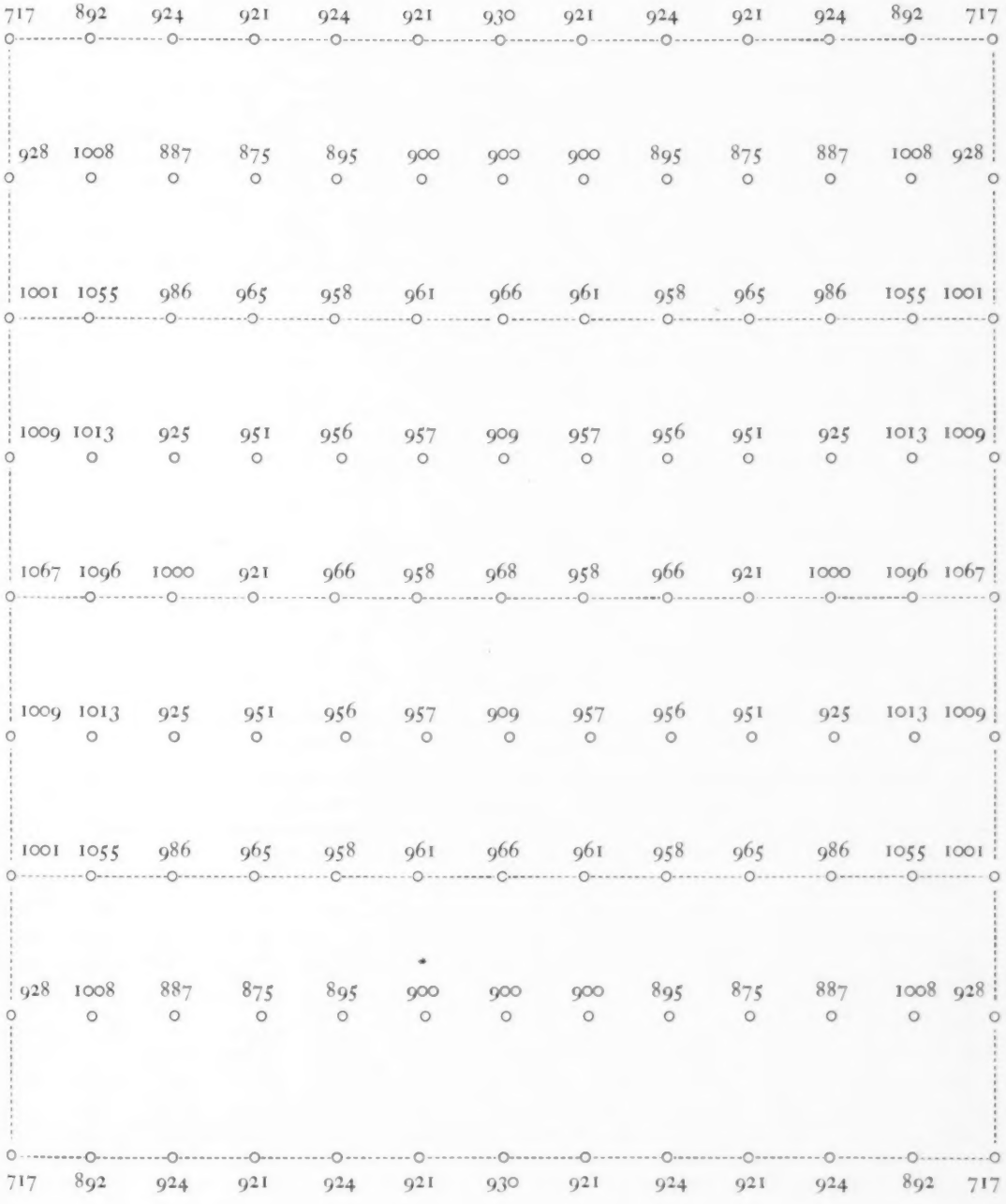


TABLE V

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(1.0 cm. enclosed cobalt 60 wire: wall diameter 0.23 mm.; wire diameter 1.0 mm.; bore diameter 1.19 mm.; over-all diameter 1.65 mm.)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center												
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
0.5	40.81	28.23	11.39	5.33	2.97	1.87	1.24	0.93	0.70	0.55	0.44	0.36	0.30
1.0	12.19	10.10	6.62	4.06	2.47	1.76	1.25	0.93	0.73	0.56	0.45	0.33	0.31
1.5	5.59	5.09	3.98	2.90	2.12	1.52	1.14	0.88	0.69	0.55	0.45	0.37	0.31
2.0	3.20	3.01	2.60	2.08	1.64	1.27	0.99	0.79	0.62	0.53	0.43	0.36	0.31
2.5	2.06	1.98	1.78	1.53	1.27	1.04	0.85	0.70	0.58	0.48	0.40	0.35	0.29
3.0	1.43	1.40	1.30	1.15	1.00	0.85	0.72	0.61	0.51	0.44	0.37	0.32	0.28
3.5	1.06	1.04	0.98	0.90	0.80	0.70	0.61	0.53	0.46	0.40	0.34	0.30	0.26
4.0	0.81	0.81	0.77	0.71	0.65	0.58	0.52	0.46	0.40	0.37	0.31	0.28	0.25
4.5	0.64	0.63	0.61	0.58	0.54	0.50	0.44	0.40	0.36	0.32	0.29	0.25	0.23
5.0	0.52	0.51	0.50	0.48	0.45	0.42	0.38	0.35	0.32	0.29	0.26	0.23	0.21
5.5	0.43	0.42	0.42	0.40	0.39	0.36	0.33	0.31	0.28	0.26	0.23	0.21	0.19
6.0	0.36	0.36	0.35	0.34	0.33	0.31	0.29	0.27	0.25	0.23	0.21	0.19	0.18
6.5	0.31	0.31	0.30	0.29	0.28	0.27	0.27	0.24	0.22	0.21	0.19	0.18	0.15
7.0	0.26	0.26	0.26	0.25	0.25	0.24	0.23	0.21	0.20	0.19	0.17	0.16	0.15
7.5	0.23	0.23	0.23	0.22	0.22	0.21	0.20	0.19	0.18	0.17	0.16	0.15	0.14
8.0	0.20	0.20	0.20	0.20	0.19	0.19	0.18	0.17	0.16	0.16	0.15	0.14	0.13

TABLE VI

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(2.0 cm. enclosed cobalt 60 wire: wire diameter 1.0 mm.; wall thickness 0.23 mm.; bore diameter 1.19 mm.; over-all diameter 1.65 mm.)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center											
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5
0.5	28.23	26.10	16.74	7.13	3.56	2.10	1.36	0.94	0.70	0.53	0.42	0.33
1.0	10.11	9.41	7.08	4.60	2.91	1.93	1.33	0.98	0.74	0.58	0.45	0.36
1.5	5.13	4.78	3.99	3.05	2.26	1.63	1.19	0.88	0.71	0.56	0.46	0.37
2.0	3.01	2.90	2.54	2.12	1.67	1.31	1.03	0.80	0.66	0.52	0.44	0.36
2.5	1.98	1.92	1.75	1.52	1.28	1.06	0.87	0.71	0.58	0.49	0.41	0.34
3.0	1.40	1.36	1.27	1.15	1.00	0.85	0.72	0.61	0.52	0.44	0.37	0.32
3.5	1.03	1.02	0.96	0.89	0.79	0.71	0.61	0.53	0.46	0.40	0.34	0.29
4.0	0.80	0.79	0.75	0.71	0.65	0.58	0.52	0.46	0.41	0.35	0.31	0.28
4.5	0.64	0.63	0.60	0.57	0.53	0.49	0.45	0.40	0.35	0.31	0.28	0.25
5.0	0.51	0.50	0.49	0.47	0.45	0.42	0.37	0.34	0.31	0.28	0.25	0.23
5.5	0.43	0.42	0.41	0.40	0.37	0.35	0.32	0.30	0.28	0.26	0.23	0.22
6.0	0.35	0.35	0.34	0.33	0.32	0.30	0.29	0.27	0.25	0.23	0.21	0.19
6.5	0.30	0.30	0.29	0.29	0.28	0.27	0.25	0.24	0.22	0.20	0.19	0.17
7.0	0.26	0.26	0.25	0.25	0.24	0.24	0.22	0.21	0.20	0.19	0.18	0.17
7.5	0.23	0.23	0.22	0.22	0.21	0.21	0.20	0.19	0.18	0.17	0.16	0.15
8.0	0.20	0.20	0.19	0.19	0.19	0.18	0.18	0.17	0.16	0.16	0.15	0.14

Table VII

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(3.0 cm. enclosed cobalt 60 wire: wire diameter 1.0 mm.; wall thickness 0.23 mm.; bore diameter 1.19 mm.; over-all diameter 1.65 mm.)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center										
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
0.5	21.19	20.58	18.37	11.76	5.06	2.66	1.49	1.06	0.76	0.56	0.43
1.0	8.48	8.09	7.13	5.31	3.38	2.24	1.37	1.07	0.80	0.61	0.49
1.5	4.52	4.36	3.90	3.17	2.41	1.76	1.31	0.98	0.73	0.59	0.48
2.0	2.79	2.70	2.48	2.12	1.74	1.38	1.08	0.87	0.68	0.55	0.45
2.5	1.88	1.84	1.70	1.52	1.30	1.09	0.90	0.74	0.61	0.51	0.43
3.0	1.33	1.31	1.24	1.14	1.00	0.87	0.74	0.63	0.53	0.46	0.39
3.5	1.01	0.99	0.95	0.88	0.80	0.71	0.63	0.54	0.47	0.41	0.35
4.0	0.78	0.77	0.75	0.70	0.65	0.58	0.53	0.47	0.42	0.36	0.32
4.5	0.63	0.61	0.60	0.57	0.53	0.49	0.45	0.41	0.36	0.32	0.29
5.0	0.50	0.50	0.49	0.47	0.45	0.42	0.39	0.34	0.32	0.28	0.26
5.5	0.42	0.42	0.41	0.40	0.37	0.35	0.33	0.30	0.28	0.26	0.24
6.0	0.35	0.35	0.34	0.33	0.32	0.31	0.29	0.27	0.25	0.23	0.22
6.5	0.30	0.30	0.29	0.29	0.28	0.27	0.25	0.24	0.22	0.21	0.19
7.0	0.26	0.26	0.26	0.25	0.25	0.23	0.23	0.21	0.20	0.19	0.18
7.5	0.23	0.23	0.23	0.22	0.22	0.21	0.20	0.19	0.18	0.17	0.16
8.0	0.20	0.20	0.20	0.19	0.19	0.19	0.18	0.17	0.17	0.16	0.15

Table VIII

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(4.0 cm. enclosed cobalt 60 wire: wire diameter 1.0 mm.; wall thickness 0.23 mm.; bore diameter 1.19 mm.; over-all diameter 1.65 mm.)

Cm. from Tube	Distance along Tube Axis: Cm. from Center									
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
0.5	16.74	16.61	15.87	14.00	9.03	3.94	2.11	1.21	0.87	0.54
1.0	7.08	7.01	6.51	5.58	4.21	2.71	1.81	1.14	0.90	0.59
1.5	3.99	3.91	3.39	3.20	2.60	1.98	1.46	1.09	0.82	0.63
2.0	2.54	2.50	2.35	2.11	1.78	1.46	1.17	0.92	0.73	0.58
2.5	1.75	1.72	1.64	1.49	1.31	1.12	0.94	0.77	0.65	0.52
3.0	1.27	1.25	1.20	1.11	1.00	0.88	0.76	0.65	0.55	0.47
3.5	0.96	0.96	0.92	0.87	0.79	0.71	0.63	0.55	0.48	0.42
4.0	0.75	0.75	0.72	0.69	0.64	0.58	0.52	0.47	0.42	0.37
4.5	0.60	0.60	0.58	0.56	0.52	0.49	0.45	0.41	0.36	0.32
5.0	0.49	0.49	0.48	0.46	0.44	0.41	0.37	0.35	0.31	0.29
5.5	0.41	0.42	0.40	0.39	0.36	0.36	0.32	0.31	0.28	0.27
6.0	0.34	0.34	0.34	0.33	0.32	0.30	0.29	0.27	0.25	0.23
6.5	0.29	0.29	0.29	0.28	0.27	0.26	0.25	0.24	0.22	0.21
7.0	0.26	0.26	0.25	0.25	0.24	0.23	0.22	0.21	0.20	0.19
7.5	0.23	0.23	0.22	0.22	0.21	0.21	0.20	0.19	0.18	0.17
8.0	0.20	0.20	0.19	0.19	0.19	0.18	0.18	0.17	0.16	0.15

TABLE IX

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(5.0 cm. enclosed cobalt 60 wire: wire diameter 1.0 mm.; wall thickness 0.23 mm.; bore diameter 1.19 mm.; over-all diameter 1.65 mm.)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center								
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
0.5	13.87	13.76	13.48	12.87	11.32	7.32	3.23	1.74	1.01
1.0	6.12	6.02	5.79	5.39	4.61	3.47	2.25	1.52	0.97
1.5	3.56	3.49	3.36	3.12	2.70	2.18	1.67	1.24	0.94
2.0	2.34	2.29	2.20	2.03	1.80	1.54	1.25	1.00	0.79
2.5	1.64	1.62	1.55	1.45	1.28	1.15	0.98	0.82	0.68
3.0	1.20	1.19	1.15	1.08	0.99	0.89	0.78	0.68	0.57
3.5	0.93	0.91	0.89	0.84	0.78	0.71	0.64	0.54	0.49
4.0	0.73	0.72	0.71	0.67	0.64	0.58	0.53	0.48	0.43
4.5	0.59	0.58	0.57	0.55	0.52	0.49	0.45	0.41	0.37
5.0	0.48	0.48	0.45	0.45	0.43	0.41	0.39	0.35	0.32
5.5	0.42	0.40	0.40	0.39	0.36	0.34	0.33	0.30	0.29
6.0	0.33	0.34	0.32	0.32	0.31	0.30	0.29	0.27	0.25
6.5	0.29	0.29	0.29	0.28	0.27	0.26	0.25	0.24	0.22
7.0	0.26	0.25	0.25	0.24	0.24	0.23	0.22	0.21	0.20
7.5	0.23	0.22	0.22	0.22	0.21	0.20	0.19	0.19	0.18
8.0	0.20	0.20	0.19	0.19	0.19	0.18	0.18	0.17	0.16

TABLE X

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(6.0 cm. enclosed cobalt 60 wire: wire diameter 1.0 mm.; wall thickness 0.23 mm.; bore diameter 1.19 mm. over-all diameter 1.65 mm.)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center							
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
0.5	11.76	11.71	11.61	11.33	10.80	9.49	6.15	2.73
1.0	5.31	5.26	5.16	4.94	4.58	3.91	2.95	1.93
1.5	3.17	3.15	3.06	2.91	2.49	2.33	1.88	1.44
2.0	2.12	2.11	2.04	1.94	1.78	1.57	1.33	1.09
2.5	1.52	1.50	1.46	1.39	1.28	1.16	1.01	0.87
3.0	1.14	1.13	1.09	1.04	0.97	0.89	0.79	0.70
3.5	0.88	0.88	0.84	0.81	0.81	0.71	0.62	0.57
4.0	0.70	0.70	0.68	0.66	0.61	0.58	0.53	0.49
4.5	0.57	0.56	0.55	0.53	0.51	0.48	0.45	0.41
5.0	0.47	0.47	0.46	0.44	0.43	0.41	0.37	0.35
5.5	0.40	0.40	0.39	0.39	0.36	0.34	0.33	0.31
6.0	0.33	0.33	0.33	0.31	0.31	0.30	0.28	0.27
6.5	0.29	0.29	0.28	0.28	0.27	0.26	0.25	0.23
7.0	0.25	0.25	0.24	0.24	0.23	0.23	0.22	0.21
7.5	0.22	0.22	0.22	0.21	0.21	0.20	0.19	0.19
8.0	0.20	0.19	0.19	0.19	0.19	0.18	0.18	0.17

Table XI

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(1.0 cm. enclosed cobalt 60 capsule; diameter 4.0 mm.; filter 2.0 mm. brass)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center												
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
0.5	34.74	23.84	9.33	4.44	2.60	1.62	1.13	0.83	0.64	0.50	0.41	0.34	0.28
1.0	10.37	8.59	5.46	3.28	2.06	1.39	1.04	0.77	0.60	0.48	0.39	0.32	0.27
1.5	4.79	4.37	3.36	2.39	1.72	1.20	0.90	0.70	0.55	0.45	0.36	0.31	0.25
2.0	2.74	2.59	2.20	1.73	1.33	1.01	0.80	0.65	0.50	0.42	0.34	0.29	0.25
2.5	1.76	1.72	1.54	1.28	1.06	0.84	0.69	0.56	0.47	0.40	0.32	0.27	0.23
3.0	1.23	1.20	1.11	0.98	0.83	0.70	0.58	0.49	0.42	0.35	0.30	0.26	0.22
3.5	0.91	0.90	0.84	0.76	0.67	0.58	0.50	0.44	0.37	0.32	0.27	0.24	0.22
4.0	0.70	0.69	0.66	0.61	0.54	0.50	0.43	0.37	0.33	0.30	0.27	0.22	0.20
4.5	0.55	0.54	0.53	0.50	0.45	0.41	0.39	0.33	0.29	0.26	0.23	0.21	0.19
5.0	0.45	0.45	0.43	0.41	0.37	0.35	0.33	0.29	0.26	0.24	0.21	0.19	0.17
5.5	0.37	0.36	0.35	0.33	0.30	0.29	0.28	0.26	0.23	0.21	0.20	0.18	0.16
6.0	0.31	0.31	0.30	0.29	0.27	0.26	0.25	0.23	0.21	0.21	0.18	0.16	0.15
6.5	0.26	0.26	0.26	0.25	0.24	0.23	0.22	0.20	0.19	0.18	0.16	0.15	0.14
7.0	0.23	0.23	0.22	0.22	0.21	0.20	0.19	0.18	0.17	0.16	0.15	0.14	0.12
7.5	0.20	0.20	0.20	0.19	0.19	0.18	0.17	0.17	0.16	0.15	0.14	0.12	0.11
8.0	0.18	0.18	0.18	0.17	0.17	0.16	0.16	0.15	0.14	0.12	0.12	0.11	0.10

Table XII

GAMMA ROENTGENS PER MILLICURIE HOUR DELIVERED AT VARIOUS DISTANCES FROM VARIOUS POINTS ALONG LINEAR COBALT 60 SOURCES

(1.0 cm. enclosed cobalt 60 capsule; diameter 4.0 mm.; lead plug at each end, 5 mm. length, 4.0 mm. diameter; filter, 2.0 mm. brass wall enclosing both cobalt capsule and lead plugs)

Cm. from Tube	Distance Along Tube Axis: Cm. from Center								
	0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
0.5	34.74	23.84	8.56	3.37	1.78	1.17	0.74	0.59	0.46
1.0	10.37	8.59	5.46	3.15	1.86	1.17	0.77	0.57	0.44
1.5	4.79	4.37	3.35	2.38	1.56	1.14	0.79	0.59	0.45
2.0	2.74	2.59	2.20	1.74	1.31	1.00	0.73	0.58	0.45
2.5	1.76	1.72	1.54	1.28	1.04	0.85	0.67	0.54	0.43
3.0	1.23	1.20	1.11	0.98	0.84	0.71	0.58	0.48	0.40
3.5	0.91	0.90	0.84	0.76	0.67	0.59	0.49	0.43	0.36
4.0	0.70	0.69	0.66	0.61	0.55	0.50	0.44	0.37	0.33
4.5	0.55	0.54	0.53	0.50	0.46	0.41	0.37	0.33	0.29
5.0	0.45	0.45	0.43	0.41	0.39	0.35	0.32	0.29	0.26
5.5	0.37	0.36	0.35	0.34	0.33	0.30	0.27	0.26	0.24
6.0	0.31	0.31	0.30	0.29	0.28	0.26	0.23	0.23	0.20
6.5	0.26	0.26	0.26	0.25	0.25	0.23	0.20	0.20	0.19
7.0	0.23	0.22	0.22	0.22	0.21	0.20	0.19	0.18	0.17
7.5	0.20	0.20	0.20	0.19	0.19	0.18	0.17	0.17	0.15
8.0	0.18	0.18	0.17	0.17	0.17	0.16	0.16	0.15	0.14

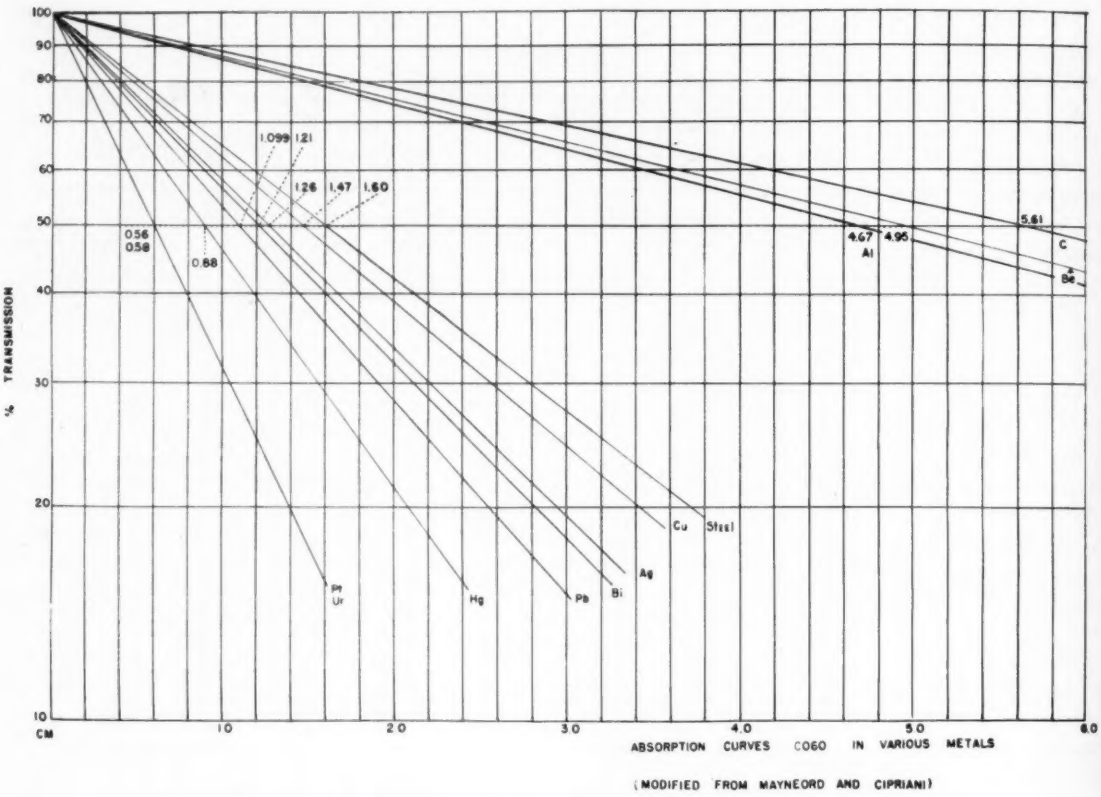


FIG. 1. Representative experimentally determined absorption curves for cobalt 60 (modified from Mayneord and Cipriani, 1947).

distribution schemes, and reasonably good homogeneity is obtained.

Tables are also presented which indicate the dosage delivered in gamma roentgens per millicurie hour around linear sources 1 mm. in diameter and 1 to 6 cm. in length when encased in 16 gauge hyperchrome steel; and for sources 4 mm. in diameter and 1 cm. in length when encased in 2 mm. brass.

An additional table is presented for use with a 2 mm. brass capsule which contains a 1 cm. by 4 mm. cylinder of cobalt 60 with a 5 by 4 mm. cylinder of lead at each end.

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DISCUSSION

DR. GILBERT H. FLETCHER, Houston, Texas. In a previous publication, the author reported noticeably stronger reactions in cobalt 60 implants over radium implants performed in similar conditions. However, two factors were not entirely controlled: size of area irradiated and time of irradiation.

The active lengths of the cobalt 60 and radium needles were respectively 2 cm. and 1.5 cm. Using needles of 1.5 cm. active length in a 2 by 2 cm. area would result in the corners receiving lower dosages when compared to the dosage using 2 cm. active length needles. A difference in the size of areas of equal dosage may be significant, especially for an implant of 4 square centimeters, the severity of reaction increasing with the size of the area treated.

The average time of irradiation for radium was 105 hours and eighty-three hours for cobalt 60. In addition, due to the lack of half strength cobalt 60 needles, the center needle of the cobalt 60 implant was removed after forty hours, which means that during the first forty hours the cobalt 60 implant was of a much higher intensity. These two factors are additive to produce more severe reactions in favor of cobalt 60, and no conclusions about the difference in biological effectiveness can be drawn until all factors are identical.

In the present study, the author has controlled very adequately time factor and size of area. The difference in severity of reaction is much less, showing that some of the difference in the previous series of experiments was due to area and time factor.

The factors other than area, time, and fractionation, which may be responsible for the difference in biological results between equal doses of cobalt 60 and radium gamma rays, calculated on an "in air" basis, are:

(1) Difference in behavior of cobalt 60 and radium gamma radiation in a scattering medium, *i.e.*, a difference in the ratio

$$\frac{\text{dose rate in scattering medium}}{\text{dose rate in air}}.$$

(2) Differences in biological efficiency between cobalt 60 and radium gamma radiation.

(3) Differences in the shape of isodose curves for sources of equal length. (This would change the effective treated areas for implants and molds of nominally identical area.)

The effects considered under heading (1) above have been investigated at this Institution and by Van Dilla and Hine (*Nucleonics*, July, 1952), and the gamma radiations from cobalt 60 and from radium are found to behave in much the same way, *i.e.*, the ratio

$$\frac{\text{dose rate in scattering medium}}{\text{dose rate in air}}$$

is the same in the case of cobalt and radium gamma radiation at different distances from the source.

Differences in biological efficiency between cobalt 60 and radium gamma radiation would appear to be very unlikely, if it is acknowledged that the biological efficiency of irradiation is a function of the ion density produced by this irradiation. Work of Cormack and Johns (*Brit. J. Radiol.*, July, 1952) shows that the ion density in water due to cobalt 60 and radium gamma-radiation is substantially identical. Similar relative results have been obtained by Gray (*Brit. J. Radiol.*, Suppl. 1, 1947), though there is a difference in absolute values in ion density between the two calculations due to a difference in the averaging employed.

On experimental as well as theoretical grounds it would appear therefore to be very unlikely that a change from radium gamma radiation to cobalt gamma radiation would produce a marked change in biological efficiency.

We have started to investigate point (3) at our institution by taking measurements with a scintillation counter around radium and cobalt 60 sources of the same active length. Isodose curves were also measured with an automatic isodose curve recorder. The ratio of the cobalt to the radium dosage rate increases in areas where the oblique filtration is important—particularly at and beyond the end of the active length of the source. Calculations based on self-absorption and oblique filtration agree substantially with measured data. In other words, the added self-absorption and the oblique filtration of the steel sheaths is less than the oblique filtration of the platinum.

In comparing linear sources of cobalt 60 and radium, the following conclusions can be drawn:

(1) There is an increase in the difference in dosage rate of cobalt 60 over radium needles close to the source. This effect will be exaggerated for longer active length needles.

(2) Since the isodose curves at the ends of the needles for cobalt 60 sources do not show such marked effects of oblique filtration and end effect, they therefore enclose a larger area than those of a radium source.

This means that a single conversion factor may not be adequate. We are now in the process of investigating the practical significance of this difference in various modalities of gamma-ray therapy.

Dr. Meschan's paper is a stimulating report that points the way for more detailed studies.

DR. MESCHAN (closing). Thank you very much, Dr. Fletcher. I do appreciate these additional physical data, and I think in general they would seem to bear out further some of the very points that were presented in the paper.

I believe we can predict quite well that the isodose curves will be slightly different, as our calculated values also have indicated. I would say that there were many calculated data included in the paper prepared for publication, which I did not present here, to avoid further confusion of the issue.

We have applied cobalt 60 clinically in some 75 cases in almost every type of interstitial and intercavitary and external plaque-like application, and in general I feel that one can probably go ahead and use it very much as radium, with the additional correction factors as indicated here.

In general, we have found no problems involved in making the slight additional correction in favor of cobalt 60 until these further isodose curves can be carried out and carefully compared with the calculated values.

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THE ELECTRON SPECTRA PRODUCED BY A COBALT 60 SOURCE IN WATER

By EVANS HAYWARD
National Bureau of Standards
WASHINGTON, D.C.

ENERGY is absorbed from a beam of photons by photoelectric effect, Compton scattering, or pair production. For low atomic number materials and energies between 100 kev. and 1 mev. Compton scattering is the most important process, and multiple Compton scattering is responsible for the gradual piling up of photons at the low energy end of the spectrum. As we go deeper into the material, the average energy of the photons decreases and finally they are absorbed by the photoelectric effect. These problems of the diffusion and degradation of roentgen rays have been studied by Spencer and Fano,[2] and Spencer and Stinson.[3]

A series of experiments associated with the theoretical work at the National Bureau of Standards was begun a few years ago. The first experiment[4] was one in which the total radiation intensity was measured as a function of the distance from a gamma-ray source in a large tank of water with an ionization chamber. The results were found to agree with the theoretical predictions very well. The experiment described here, and reported more completely elsewhere,[1] was undertaken as a further check on the theory. The problem was in effect to measure how many secondary electrons of what energies are produced by a gamma-ray source in water at various penetrations. A scintillation spectrometer was designed to measure the secondary electron energy distribution from a Co^{60} source in a large tank of water. The atomic number and density of anthracene crystals are so close to those of water that, to the electrons as they are scattered in the crystal, there appears to be no transition from water to the crystal. Hence, the pulse-height distribution representing the energy lost in an anthracene crystal would correspond to the energy distribution of the electrons produced in an equal mass of water occupying the same position.

The Co^{60} source and a counting instrument were suspended near the center of the water tank from a wooden rack as shown in Figure 1. The counter consisted of the anthracene crystal, a Lucite light pipe, a photomultiplier tube, and a preamplifier. The whole unit was enclosed in an aluminum and Lucite container to protect it from the surrounding water. The Lucite light pipe separated the crystal from the photomultiplier, and a thin aluminum foil wrapped around the Lucite and anthracene crystal served as a light reflector. Thus, as the electrons are produced in the anthracene crystal, the light they produce is guided down the Lucite tube and the scintillations are detected by the photomultiplier.

The counter was designed to measure the energy of only those electrons produced in and totally absorbed by the anthracene crystal. Tests were made to ascertain that only these electrons were detected. A negligible contribution to the measured energy distribution was made by all those electrons that were created outside but scattered into the crystal and those created inside and scattered outside the crystal. Additional checks were run to determine the sensitivity of the spectrum to the length of the Lucite light tube and to the presence of a second photomultiplier tube close to the crystal. In all instances, the effects were negligible.

Six Co^{60} sources, ranging from 10^6 to 10^{11} disintegrations per second, were used at varying separations between the source and the detector. A different source was used at each separation in order to have sufficiently low counting rates and thus

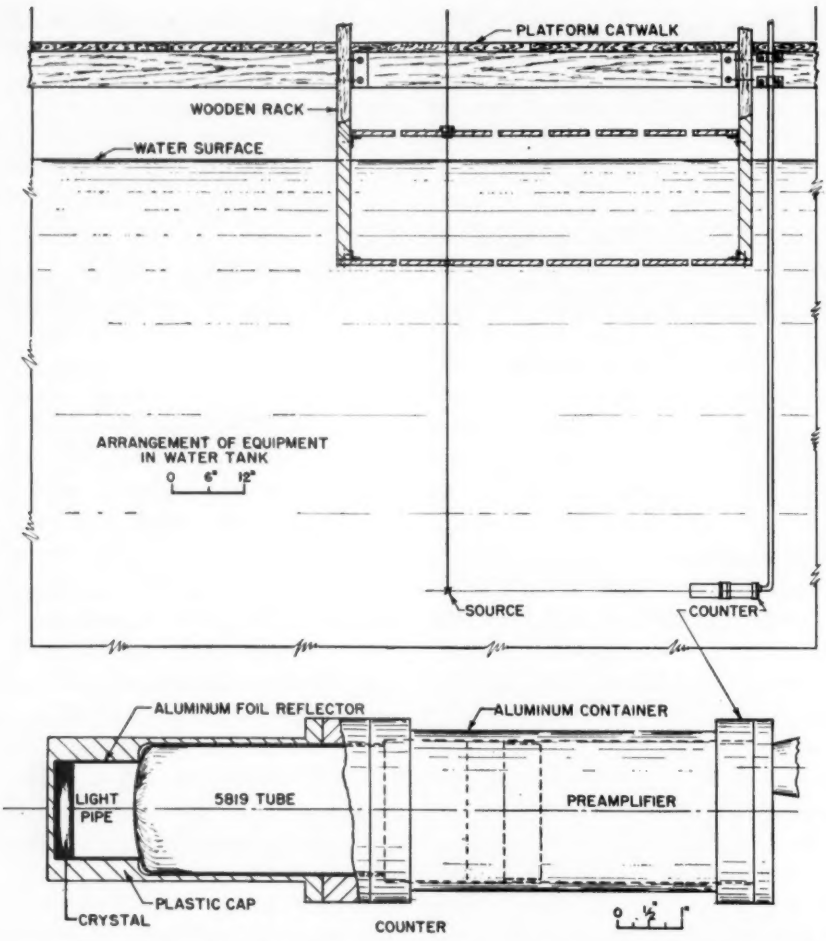

FIG. 1. Cross section (top) of the experimental setup for determining the quality of gamma radiations from radioactive cobalt.

avoid residual and accumulated effects from the very large number of low energy electrons characteristic of these spectra. The relative intensities of the sources had been measured in pairs and compared to a National Bureau of Standards cobalt standard, by which activities are known within ± 6 per cent.

The electron spectra produced by 1.17 and 1.33 mev. Co^{60} gamma rays were measured at distances of 10, 20, 41.6, 81.6, 121.6, and 161.6 cm. from the source and the results are shown in Figure 2 plotted on semi-logarithmic paper. In plotting the data, the ordinate scale was in terms of the number of electrons per mev. interval, per disintegration of the source, per gram of anthracene, and the abscissa scale was in mev. This means, for example, that at 41.6 cm. from a Co^{60} source immersed in water there are at 0.600 mev. 10^{-6} electrons /(mev. gram disintegration) or for every disintegration of the source there are in 1 gram of water $10^{-6}/100 = 10^{-8}$ electrons between 0.600 and 0.610 mev. The series of dots were obtained from the experimental data, and the solid curves from the predictions made in theories developed by Spencer and Fano.[2]

In order to express the data for the ordinate in these units, it was necessary to know not only the counting rate but also the disintegration rate of the source and the window width of the counting instrument. The error in measuring the absolute intensities was ± 10 per cent, due mostly

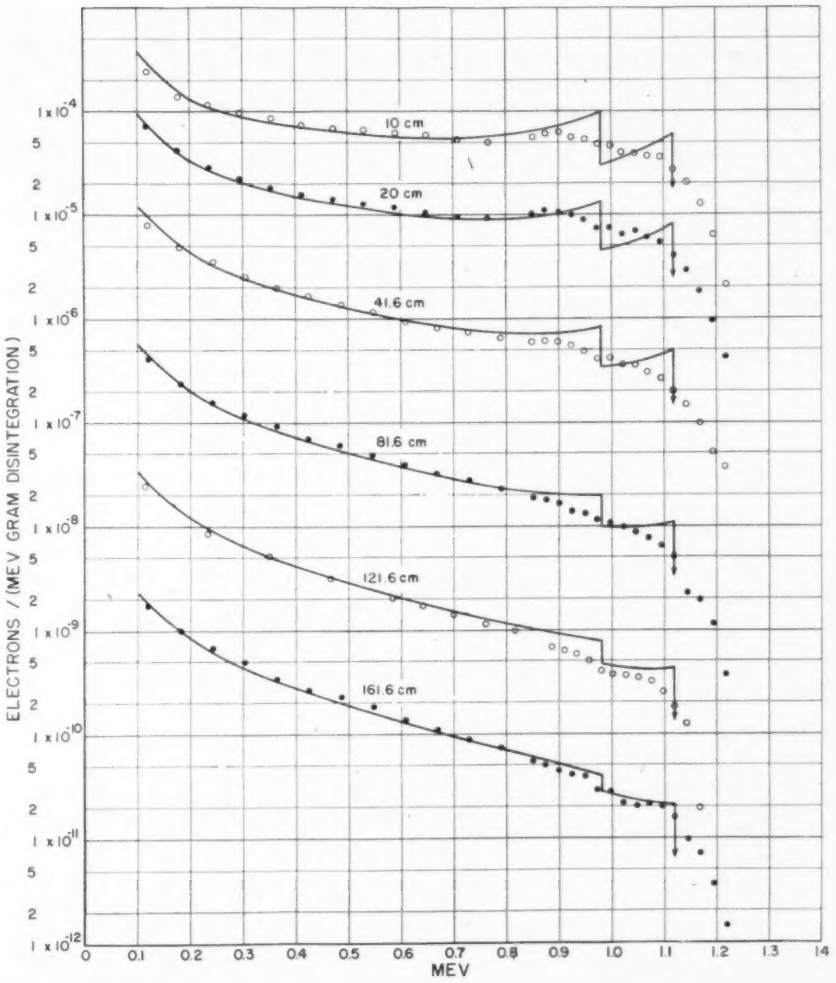

Fig. 2. The differential spectra of electrons produced by a Co^{60} source in an anthracene crystal as a function of the distance in water from the source.

to uncertainties in the determination of the latter two quantities.

The energy scale for the abscissa was obtained by making a linear plot of the data and taking the two points of inflection at the end of the spectrum as corresponding to 0.96 and 1.12 mev., the maximum energy Compton electrons that can result from the 1.17 and 1.33 mev. gamma rays. This calibration was accurate to about ± 1.5 per cent. The standard deviations based on the number of counts were all less than ± 5 per cent and almost all less than ± 3 per cent. The background was negligible because the large mass of water provided an excellent shield for stray radiation.

At 10 cm. from the source, the high energy end of the spectrum is quite intense and two peaks, corresponding to the two gamma rays, are easily recognized. At greater distances the energy loss becomes more and more concentrated in the lower energy electrons, and the rate at which the spectrum changes becomes lessened. At distances of 1 meter or more, the changes in the shape of the spectrum of these medium and hard radiations are too small to be measured with such a low resolution spectrometer.

National Bureau of Standards
Washington 25, D. C.

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Vol. 71, No. 2

THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

Editor: Lawrence Reynolds, M.D. *Assistant Editor:* Ruth Bigelow, B.S.

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Fifty-fifth Annual Meeting: Shoreham Hotel, Washington, D. C., September 21–24, 1954.

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Thirty-sixth Annual Meeting: The Homestead, Hot Springs, Virginia, March 14, 15 and 16, 1954.

EDITORIALS

MORE CONTINUOUS CARE FOR THE CANCER PATIENT

GREAT effort has been expended in teaching the laity and physicians the symptoms of cancer, the importance of detecting cancer in the early stages, the value of taking a prompt biopsy to establish an accurate diagnosis, and the institution of immediate treatment by the recognized modalities—surgery, radium, and roentgen rays. These achievements in the care of the patient with cancer have been wrought through advances made by the medical profession and through crusades by the cancer societies.

There remains, however, another phase in the care of the cancer patient which should receive greater emphasis. It is that the cancer patient should have more continuous care—not just an occasional "follow-up observation." Why more attention has not been given to this idea, it is difficult to say. Some blame may lie in the phrase, "the follow-up," which is an inadequate description of the obligations and duties which must be assumed by both the physician and the patient. To many it implies a curiosity about what has happened after the initial treatment and brings to mind columns of figures and charts on statistics of cures and survivals. While the accumulation of this knowledge is very necessary, the phrase fails to suggest that the more vital task is to provide the cancer patient with continuous care or at least a continuous pattern of frequent examinations and treatments.

The radiologist understands and values a program of continuous care more than most physicians because he must see and treat those unfortunate patients with advanced untreated recurrences and metastases. Many of them could have been treated weeks or even months earlier at a time when they could have been given effective palliative therapy and returned to work at their occupation for months or occasionally years. Such instances are evidence of negligence—either the physician failed to examine the patient carefully and at frequent enough intervals or the patient failed to return at the designated time.

The patient returning with an initial large recurrence or with extensive and widespread metastases has not received continuous care. Thus the size and magnitude of the first recurrence or metastasis becomes an index of the degree of attention and care the cancer patient has received. It is a direct reflection of the professional competence of the physician and of the cooperativeness of the patient. The failure of the profession to provide and insist upon a program of continuous care has been overlooked too long. The establishing of the concept of "continuous care" for the cancer patient warrants an educational campaign for the laity and for the medical profession. After all, most cancer patients sooner or later require palliative treatment and it should be recognized in the early stages—not in the terminal stages.

A prearranged plan of continuous care is essential if recurrences and metastases are to be found in the early stages when they can be treated effectively and the patient temporarily salvaged. The opportune time to explain and outline the plan to the patient is on completion of the treatment of the primary tumor. The patient is then receptive to suggestions as he is thinking about the future. It can be presented in an optimistic manner much as one undertakes an insurance program. The concept of fre-

quent examinations and continuous care is comparable to the necessity of paying premiums on insurance. The periodicity of the examinations will depend on the type and extent of the primary tumor, but it must be more frequent than is now practiced.

Of equal concern is a program of continuous care for the patient with known recurrences or metastases, or both, as his comfort and usefulness are even more dependent on the prompt detection of new metastases and their immediate control whenever practicable.

The radiologists are the group to initiate a campaign to promote an intelligent understanding of the problem of continuous care for cancer patients in order that the laity and the physician may be diligent in detecting the early recurrence or metastasis. The American public must be taught that cancer in the great majority of instances is controllable and then only through continuous care exercised by both the physician and the patient.

Wendell G. Scott, M.D.

35 North Central Ave.
Clayton 5, Missouri

JOHN JAY MOORE
1888–1953

JOHN JAY MOORE, Colonel, Medical Corps, U. S. Army, retired, died from a heart condition in San Antonio, Texas, on July 30, 1953.

Born November 12, 1888, Colonel Moore was a native of Fremont, Ohio. He received his M.D. degree from Ohio State University in 1912. During the early phases of World War I, he was assigned to postgraduate training at the Army Medical School; thereafter to specialized training in radiology at the University of Pennsylvania, under Dr. Henry K. Pancoast.

John Jay Moore began his military

career in 1917 when he was commissioned First Lieutenant in the Regular Army. His start with radiology was in 1919. His conscientious and scientific attitude and enthusiasm were quickly recognized both by the Army and the profession at large; so much so that his assignments were progressively as Chief of Radiological Service in leading Army institutions; during the remainder of World War II, at base hospitals, then at the Letterman Army Hospital in San Francisco, Gorgas Hospital in the Canal Zone, a return tour at the Letterman Army Hospital, then as Director of Radiology at the Army Medical School in Washington, D. C., Chief of the Radiological Service at Walter Reed Army Hospital, a third tour at Letterman Army Hospital, and a tour at Tripler Hospital in Honolulu.

During World War II, he established and commanded the Medical Department Enlisted Technicians School at Fort Sam Houston, Texas, and at Fort Benjamin Harrison, Indiana. He was Commandant at the School for Medical Department Technicians at Fitzsimons Army Hospital, Denver, Colorado, when he retired for physical disability in September, 1947, after over thirty years of service.

Colonel Moore always recognized the importance of participating in group conferences locally, and he maintained the foresight of continually improving his prospective of the specialty of radiology by affiliation and active participation with radiological organizations. He was the first radiologist in the Army to be certified by the American Board of Radiology; this recognition was attained in 1934. After becoming a diplomate of the American Board of Radiology he was elected to Fellowship in the American College of Radiology. He was very proud of his membership in the American Roentgen Ray Society—to which he was elected in 1932. During 1935–1936 he held the office of First Vice-President in this organization. He was also a Fellow of the American College of Surgeons and a member of the American Medical Association.

Colonel Moore's main interests included scientific medicine, his family and social life and, until the last ten or fifteen years, a fast strategic game of tennis.

Colonel Moore is survived by his wife, Mrs. Persis Moore of San Antonio, Texas; a daughter, Mrs. Barbara Holms; his mother, Mrs. W. O. Moore and a sister, Mrs. William E. Russell, both of Fremont, Ohio.

A brilliant doctor, soldier and teacher, Colonel Moore will be greatly missed both professionally and personally by his host of friends.

A. A. de Lorimier, M.D.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

MEETINGS OF ROENTGEN SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Shoreham Hotel, Washington, D.C., Sept. 21–24, 1954.

AMERICAN RADIUM SOCIETY
Secretary, Dr. R. E. Fricke, Mayo Clinic, Rochester, Minn. Annual meeting: The Homestead, Hot Springs, Virginia, March 14–16, 1954.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: 1954, to be announced.

AMERICAN COLLEGE OF RADIOLOGY
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual meeting: 1954, to be announced.

FIFTH INTER-AMERICAN CONGRESS OF RADIOLOGY
General Secretary, Dr. Eugene P. Pendergrass, 3400 Spruce St., Philadelphia 4, Pa. Meets at Shoreham Hotel, Washington, D. C., April 24–30, 1955.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

ARIZONA RADIOLOGICAL SOCIETY
Secretary, Dr. R. Lee Foster, 507 Professional Bldg., Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Albert A. Rayle, Jr., 478 Peachtree St., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. J. J. Daversa, 345 75th St., Brooklyn, N. Y. Meets monthly fourth Tuesday, October through April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse N. Y. Meets January, May, November.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. F. A. Riebel, 15 West Goodale St., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, December, February, April, and June at Columbus Athletic Club, Columbus, Ohio.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. Elbert K. Lewis, 6337 S. Harvard Ave., Chicago, Ill. Meets second Thursday of each month, October to April inclusive at the University Club.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. Mortimer Lubert, 10515 Carnegie Ave., Cleveland 6, Ohio. Meetings at 6:45 P.M. on fourth Monday of each month from October to April.

COLORADO RADIOLOGICAL SOCIETY
Secretary, Dr. Parker Allen, Children's Hospital, Denver, Colo. Meets third Friday of each month at University of Colorado Medical Center or at Denver Athletic Club.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. E. W. Godfrey, 1676 Boulevard, West Hartford, Conn. Meets second Friday October and April.

DALLAS-FORT WORTH ROENTGEN STUDY CLUB
Secretary, Dr. O. H. Grunow, 650 Fifth Ave., Fort Worth, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. F. Lang, Harper Hospital, Detroit, Mich. Meets monthly first Thursday, October to May, at Wayne County Medical Society Building.

EAST BAY ROENTGEN SOCIETY
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. H. G. Reaves, Medical Arts Bldg., Sarasota, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. Robert M. Tankesley, 218 Doctors Bldg., Atlanta, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. E. H. Bryson, 273 Alhambra Circle, Coral Gables, Fla. Meets third Wednesday of each month at Veterans Administration Building.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. Harry Fishbein, 324 Medical Arts Bldg., Houston 2, Texas. Meets fourth Monday each month at Hermann Hospital.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Alfred M. Stone, St. Lukes Hospital, Boise, Idaho. Meets annually at same time as Idaho State Medical Association.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. William M. Loehr, 712 Hume-Mansur Bldg., Indianapolis 4. Meets second Sunday in May.

IOWA RADIOLOGICAL SOCIETY
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Willis L. Beeler, M.D., 700 Kansas Ave., Topeka, Kansas. Meets in spring with State Medical Society, and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Solomon Maranov, 1450 51st St., Brooklyn 19, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. George Jacobson, 1200 N. State St., Los Angeles 33, Calif. Meets second Wednesday each month at Los Angeles County Medical Association Building, Los Angeles.

* Secretaries of societies are requested to send timely information promptly to the Editor.

Maine Radiological Society
Secretary, Dr. Jack Spencer, Maine General Hospital, Portland 4, Maine. Meets in early spring, June and fall.

Maryland Radiological Society
Secretary-Treasurer, Dr. H. Leonard Warres, 2337 Eutaw Place, Baltimore 17, Maryland.

Miami Valley Radiological Society
Secretary, Dr. G. A. Nicoll, 134 Apple St., Dayton, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. T. J. Pfeffer, 839 N. Marshall St., Milwaukee 2, Wis. Meets monthly on second Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. John R. Hodgson, Mayo Clinic, Rochester, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. John W. Evans, 117 N. President St., Jackson, Miss. Meets third Thursday of each month at the Rotisserie Restaurant at 6:30 P.M.

Montana Radiological Society
Secretary, Dr. Grant P. Raitt, Suite 413 Medical Arts Bldg., Billings, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Frank Huber, Hempstead, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Stanley M. Wyman, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Harvard Club.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. J. R. Freid, 1049 Park Ave., New York 28, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. W. C. Sternbergh, Charlotte Memorial Hospital, Charlotte, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings by announcement.

Northeastern New York Radiological Society
Secretary, Dr. D. H. Baxter, Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesdays of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. H. B. Stewart, 2920 Capitol Ave., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. M. M. Thompson, 316 Michigan St. Toledo, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. John R. Danstrom, Medical Arts Bldg., Oklahoma City, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. J. W. Loomis, 919 Taylor St. Bldg., Portland 5, Oregon. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse 416 Pine St., Williamsport. Next annual meeting at Bedford Springs Hotel, Bedford, Penna., May 14 and 15, 1954.

Philadelphia Roentgen Ray Society
Secretary, Dr. H. M. Stauffer, Temple University Hospital, Philadelphia 40, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Donald H. Rice, Western Pennsylvania Hospital, Pittsburgh 24, Pa. Meets 6:00 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Radiological Section, Baltimore Medical Society
Secretary, Dr. H. Leonard Warres, 2337 Eutaw Place, Baltimore 17, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Connecticut Medical Society
Secretary, Dr. William A. Goodrich, 185 Jefferson St., Hartford 6, Conn. Meetings are held bi-monthly.

Radiological Section, Medical Society of the District of Columbia
Secretary, Dr. A. C. Wyman, 5445—28th St., N.W., Washington, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of Greater Cincinnati
Secretary, Dr. Chapin Hawley, 927 Carew Tower, Cincinnati 2, Ohio. Meets monthly from September to June on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. P. S. Arthur, Young Hotel Bldg., Honolulu 13, T. H. Meets third Friday of each month at a place designated by the Secretary.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. J. T. Brierre, 700 Audubon Bldg., New Orleans. Meets annually during Louisiana State Medical Society Meeting.

Radiological Society of New Jersey
Secretary, Dr. Salomon Silvera, 921 Bergen Ave., Jersey City, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of Southern California
Secretary, Dr. Donald R. Laing, 65 N. Madison Ave. Pasadena 1, Calif.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. A. Gordon Ide, 277 Alexander St., Rochester 7, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth St., Denver 7, Colo.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. Francis O. Trotter, Jr., 634 N. Grand Blvd., St. Louis 3, Mo. Meets fourth Wednesday each month, except June, July, August and September.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets Brook Army Medical Center Officers Mess first Monday of each month.

SAN DIEGO RADIOLOGICAL SOCIETY
Secretary, Dr. C. W. Bruner, 2456 Fourth Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. I. J. Miller, 2680 Ocean Avenue, San Francisco 27, Calif. Meets quarterly.

SECTION ON RADIOLOGY. CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. H. R. Morris, 1027 "D" St., San Bernardino, Calif.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. George E. Irwin, Jr., 703 N. East St., Bloomington, Ill.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Dr. J. J. McCort, Santa Clara County Hospital, San Jose, Calif. Meets second Wednesday each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. William A. Klauber, Self Memorial Hospital, Greenwood, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. G. K. Henshall, 311 Medical Arts Bldg., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort worth 4, Texas. Next meeting, Dallas, Texas, Jan. 29 and 30, 1954.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Eva L. Gilbertson, 1317 Marion St., Seattle 4, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

WEST VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. W. Paul Elkin, 515 Medical Arts Bldg., Charleston, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER RADIOLOGICAL SOCIETY
Secretary, Dr. C. G. Huntington, 170 Maple Ave., White Plains, N. Y. Meets on third Tuesdays of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY
Secretary, Dr. W. W. Moir, 309 Geele Ave., Sheboygan, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-RAY STUDY CLUB OF SAN FRANCISCO
Secretary, Dr. Wm. W. Saunders, Veterans Administration Hospital, San Francisco 21, Calif. Meets monthly, third Thursday, at 7:45 P.M., Lane Hall, Stanford University Hospital.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

SOCIEDAD MEXICANA DE RADIOLOGIA Y FISIOTERAPIA
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA
Secretary, Dr. Rafael A. Blanes, Ave. Ponce de Leon 1175, Santurce, P. R.

SOCIEDAD RADIOLÓGICA PANAMEÑA
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86, Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

BRITISH EMPIRE

BRITISH INSTITUTE OF RADIOLOGY INCORPORATED WITH THE RÖNTGEN SOCIETY
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1.

FACULTY OF RADIOLOGISTS
Honorary Secretary, Dr. J. F. Bromley, 45, Lincoln's Inn Fields, London, W.C.2, England.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

CANADIAN ASSOCIATION OF RADIOLOGISTS
Honorary Secretary-Treasurer, Dr. D. L. McRae, Suite 305, 1555 Summerhill Avenue, Montreal 25, Que. Meetings January and June.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

COLLEGE OF RADIOLOGISTS (AUSTRALIA AND NEW ZEALAND)
Honorary Secretary, Dr. Alan R. Colwell, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W.

SOUTH AMERICA

ASOCIACION ARGENTINA DE RADIOLOGIA
Secretary, Dr. Lidio G. Mocsa, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

SOCIEDAD ARGENTINA DE RADIOLOGIA, JUNTA CENTRAL, BUENOS AIRES
Secretary, Dr. Oscar F. Noguera, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

SOCIEDAD ARGENTINA DE RADIOLOGIA, FILIAL DEL LITORAL, SEDE, ROSARIO
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

SOCIEDAD ARGENTINA DE RADIOLOGIA, FILIAL DEL SUR, SEDE, LA PLATA
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

SOCIEDAD ARGENTINA DE RADIOLOGIA, FILIAL DEL CENTRO SEDE, CORDOBA
President, Prof. Dr. David L. Caro, Corro 86, Cordoba. Meets monthly.

SOCIEDAD ARGENTINA DE RADIOLOGIA, FILIAL DEL NORTE, SEDE, TUCUMAN
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza.
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av Brigadeiro Luiz Antonio, 644.

Sociedad Colombiana de Radiologia
Secretary, Dr. Luis E. Lozano B., Carrera 12 No. 20–69, 6° piso, Bogota, Colombia. Meets last Thursday of each month.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Sociedad de Radiologica, Cancerologia y Fisica Medica del Uruguay
Secretary, Dr. Arias Bellini, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Allies, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord
Secretary-General, Dr. A. Dariaux, 9 bis, Boulevard Rochechouart, Paris IX°, France.

Ceskoslovensk společnost pro rëntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10:30, X-Ray Dept., Akademia Gdansk.

Wroclaw Section Polish Society of Radiology
Secretary, Dr. R. Marciniak, Akad. Medyczna Wrocław, 68 Curie-Skłodowska St., Wrocław, Poland. Meets first Sunday of each month, X-Ray Department, Akademia Medyczna Wrocław.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Deutsche Roentgen-Gesellschaft
Secretary, Dr. Peter Kröker, (22a) Essen-Helsingen, Westpreussenstrasse 21. Meets annually in different towns.

Societa Italiana di Radiologia Medica
Secretary, Prof. Mario Ponzio, Ospedale Mauriziano. Torino, Italy. Meets biannually.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

ATOMIC ENERGY COMMISSION FELLOWSHIPS

Applications for U. S. Atomic Energy Commission Fellowships in Radiological Physics and Industrial Hygiene for the 1954–1955 school year are now being received by the Oak Ridge Institute of Nuclear Studies.

The Industrial Hygiene fellowship program supports a limited number of individuals who are studying for the master's degree in this field at the Harvard University School of Public Health and the University of Pittsburgh Graduate School of Public Health.

Radiological Physics fellowships are carried out in three separate programs as follows: at Vanderbilt University and Oak Ridge National Laboratory, at the University of Rochester and Brookhaven National Laboratory, and at the University of Washington and Hanford Works. In each case, nine months of course work at the university is followed by three months of additional study and field training at the cooperating AEC installation. Up to 25 fellows may be appointed in each of the three programs. Course work may be applied toward an advanced degree.

Basic stipend for both fellowships is $1600, with an allowance of $350 for a spouse and $350 for each dependent child. In addition, tuition and laboratory fees are paid as a part of the fellowship. Industrial Hygiene fellows may receive an additional allowance of $200 if they have already completed a year of graduate study or appropriate work experience in this field.

The two fellowship programs are supported by the Atomic Energy Commission to supply the critical need for personnel trained in these fields. Radiological Physics deals with health problems associated with the handling of radioactive materials and with the release of nuclear energy. Industrial Hygiene encompasses the usual industrial hazards in addition to those peculiar to the atomic energy program, such as the handling of radioactive wastes and flue gases and the processing of unusual and often highly toxic material.

Application forms and additional information may be obtained from the Fellowship Office, University Relations Division, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tennessee.

POSTGRADUATE COURSE IN THERAPEUTIC RADIOLOGY

The University of Southern California Medical Extension Education is presenting a course, "The Essential Physics of Therapeutic Radiology and the Clinical Applications of Radioactive Isotopes" by RobertE. Pugh, Jr., Physicist in Radiology; Paul C. Aebersold, Ph.D., Director, Isotopes Division, United States Atomic Energy Commission, Oak Ridge, Tennessee; and Henry L. Jaffe, M.D., Associate Clinical Professor of Therapeutic Radiology. This course is to be given in Los Angeles, California, March 8 through May 24, 1954, Monday evenings from 8:00 to 10:00 P.M. at the Los Angeles County Hospital and the Cedars of Lebanon Hospital. This course will provide excellent background information for those who wish also to obtain the actual clinical training necessary for AEC certification.

Additional information may be obtained from Dr. Robert S. Cleland, Medical Extension Education, School of Medicine, 2025 Zonal Ave., Los Angeles 33, California.

KANSAS RADIOLOGICAL SOCIETY

The annual meeting of the Kansas Radiological Society and greater Kansas City Radiological Society will be held at the University of Kansas Medical Center, Kansas City, Kansas, on February 15, 16, and 17, 1954. An excellent program has been arranged and interested radiologists are invited to attend.

The following guest speakers will take part in the program: Dr. Earl R. Miller, University of California, San Francisco; Mr. E. Dale Trout, Physicist, General

Electric Company; Dr. John Caffey, Columbia University, New York; Dr. Harold W. Jacox, Columbia University, New York; Dr. Clyde A. Stevenson, Scott & White Clinic, Temple, Texas; Dr. Harry M. Weber, Mayo Clinic, Rochester, Minnesota.

Further information or a program may be obtained from Dr. G. M. Tice, University of Kansas Medical Center, Kansas City 3, Kansas.

INDIAN RADIOLOGICAL ASSOCIATION

Dr. N. G. Gadekar, M.B., B.S., D.M.R.E. (Camb.), Director, Department of Radiology, Irwin Hospital, New Delhi, has been elected *President* of the Indian Radiological Association for the year 1954.

The Eighth Indian Congress of Radiology will be held in Madras from February 12 to 15, 1954.

MAINE RADIOLOGICAL SOCIETY

The newly elected officers of the Maine Radiological Society for 1954 are as follows: *President*, Dr. John D. Southworth, Togus, Maine; *Vice President*, Dr. Clark F. Miller, Lewiston, Maine; *Secretary-Treasurer*, Dr. Jack Spencer, Portland, Maine.

SAN FRANCISCO RADIOLOGICAL SOCIETY

At a recent meeting of the San Francisco Radiological Society, the following officers were elected: *President-elect*, Dr. Charles S. Capp; *Secretary-Treasurer*, Dr. Ivan J. Miller; *Member of the Executive Board*, Dr. Joseph Levitan. Dr. Maurice Robinson was installed as *President*.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor; T. LEUCUTIA, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Head

Yuhl, Eric T., Stirrett, Lloyd A., and Libby, Raymond L. A comparative study of the use of diiodofluorescein and iodinated human serum albumin for the diagnosis and localization of intracranial neoplasms. *Ann. Surg.*, Feb., 1953, *137*, 184–188.

Successful diagnosis and localization of intracranial lesions using radioactive diiodofluorescein and iodinated human serum albumin has been reported. The purpose of this study is to compare the merits of each substance.

The authors used diiodofluorescein (DIF) in examining 24 patients with suspected intracranial lesions. Seven cases had brain tumors proved at surgery. There were two false positive and two false negative tests. The over-all diagnostic accuracy was 83 per cent. In an additional 20 cases suspected of having intracranial lesions, radioactive iodinated human serum albumin (IHSA) was used. In 9 cases, brain tumors were diagnosed and verified at surgery. Two false positive tests were obtained. The over-all diagnostic accuracy of this method was 90 per cent.

The use of IHSA presented several advantages over the use of DIF. A tracer dose of 300 microcuries of IHSA yields two to three times higher counting rates than 1 millicurie of DIF. The differential uptake over the lesion compared to a normal area was 24.5 per cent with IHSA, while with DIF the differential uptake was 16.5 per cent. Whereas the variation of counts over normal symmetrical contralateral areas with DIF varied from 4.6 per cent to 12.5 per cent (mean 8.4 per cent), similar control measurements with IHSA ranged from 3.5 per cent to 9.1 per cent (mean 6.1 per cent).

When using DIF as the tracer agent, the survey must be completed within two to three hours because of the rapid excretion of this material. However, IHSA is excreted very slowly and the optimum time for measurement was found to be twenty-four hours. Repeated surveys were possible when using IHSA, while with DIF repeated measurements are difficult to do with any accuracy.

The authors conclude that while both methods give a fairly high degree of diagnostic accuracy, the tests are not reliable enough to warrant using to the exclusion of conventional diagnostic methods.—*John P. Storaasli, M.D.*

Olsson, Olle. Vertebral angiography in the diagnosis of acoustic nerve tumours. *Acta radiol.*, April, 1953, *39*, 265–272.

Of 17 patients operated on for acoustic nerve tumor since the introduction of vertebral angiography by catheterization via the radial artery, 14 were examined by means of this method. The vascular pattern varied widely from one patient to another but certain characteristics were recognized: the basilar artery was situated on the healthy side in 10; in the other 4 it showed no deviation from the midline.

In 6 patients the posterior cerebral arteries were symmetrical, or practically so. In the other 8 cases the curve of the artery on the affected side was flattened, often to a striking extent.

The superior cerebellar artery ran an unusual course in all of the cases. In 13 of the 14 cases this deviation consisted of a marked cranial displacement of the branch on the affected side.

No fewer than 9 cases showed vessels distinctly related to the tumor.—*Mary Frances Vastine, M.D.*

Garsche, R. Intrakranielle Verkalkungen als Spätfolge der Meningitis tuberculosa nach Streptomycinbehandlung. (Intracranial calcifications, a late sequel in tuberculous meningitis following streptomycin therapy.) *Fortschr. a. d. Geb. d. Röntgenstrahlen ver. m. Röntgenpraxis*, April, 1953, *78*, 391–396.

Intracranial calcifications were found in 12 of 35 children treated between 1949 and 1950. They were located in the suprasellar region, close to the midline. The calcifications appeared between three months and two years after clinical cure, in long lasting cases earlier than in cases of short duration.

They are due to an impregnation with calcium of the exudate in the basal cisterns. These changes were observed only in children under seven years of age. The clinical significance of these calcifications is not established.—*Karol E. Matzinger, M.D.*

Neck and Chest

Nash, F. A., Benjamin, B., and Lee, T. J. Detection of tuberculosis in general practice by photofluorography. *Brit. M. J.*, Feb. 7, 1953, *1*, 304–308.

A large section of London has been provided with facilities for unlimited chest photofluorography with 35 mm. films. The general practitioners in the area were circularized and requested to refer patients with a large range of symptoms for examination.

The first 3,000 cases were analyzed. Of these, 91 (3 per cent) had roentgenologically significant lesions. Sixty of the 91 patients were later classified as having active tuberculosis, this giving an over-all average of 2 per cent.

The authors conclude from their study that no evidence of a dilution (i.e., decreased incidence) would follow unlimited chest photofluorography. There was a significant increase in the incidence of tuberculosis in unmarried persons of both sexes.—*I. R. Berger, M.D.*

REICHLIN, SEYMOUR, LOVELESS, MARY H., and KANE, ERNEST G. Loeffler's syndrome following penicillin therapy. *Ann. Int. Med.*, Jan., 1953, *38*, 113–120.

The authors from Cornell University Medical College report on unusual case of a twenty-six year old white student who developed a serum sickness type of reaction associated with fever and urticaria and patchy areas of pulmonary consolidation attributed to the administration of penicillin. The patient also manifested eosinophilia which reached its height at about the same time as the pulmonary infiltrations began to clear.

It is emphasized that this is a rare type of penicillin sensitivity and it is implied that Loeffler's syndrome as we know it cannot be attributed to the administration of penicillin in most cases.—*C. L. Hinkel, M.D.*

WALDBOTT, GEORGE L. Smoker's respiratory syndrome, a clinical entity. *J.A.M.A.*, April 18, 1953, *151*, 1398–1400.

A clinical syndrome characterized by dyspnea, wheezing, constriction in the throat and upper air passages and pain in the chest associated with a tendency to frequent upper respiratory infections is described.

Of 31 patients studied, 25 were thought to have asthma and in 6 bronchiectasis was suspected. A table is included showing the important differential characteristics of "smoker's asthma" and bronchial asthma. The relationship to allergic asthma is also discussed.

It is thought possible that the condition may contribute to the development of permanent pulmonary changes such as chronic emphysema, bronchiectasis and so-called intrinsic asthma in which the etiological relationship cannot be established.—*Chauncey N. Borman, M.D.*

GOODWIN, J. F., STEINER, R. E., MOUNSEY, J. P. D., MACGREGOR, A. G., and WAYNE, E. J. A critical analysis of the clinical value of angiocardiography in congenital heart disease. *Brit. J. Radiol.*, April, 1953, *26*, 161–184.

The value of angiocardiography varies in different types of congenital heart disease. The authors have carefully examined the results in 118 cases seen in a four year period. Of these, 2 patients died, but in neither was the death directly attributable to the angiocardiographic study itself. Both were considered bad risks, and both had been subjected to an anesthetic. Each had a cerebral vascular accident.

1. The commonest congenital lesion to present for operation is tetralogy of Fallot. Of greatest importance is the demonstration of the anatomy to be encountered by the surgeon, particularly the position and number of the great vessels. One serious defect of this method of investigation was failure to visualize the types and site of pulmonary stenosis in 20 per cent of the cases. A more elaborate technique of examination will probably correct some of this difficulty. At times, when there are equivocal signs and symptoms, angiocardiography is necessary for the diagnosis.

2. Pulmonary hypertension with central cyanosis is at times the only diagnosis possible with clinical methods. It is possible to differentiate this group by angiocardiography and cardiac catheterization into "the Eisenmenger group," atrial septal defect with right to left shunt, and patent ductus arteriosus with right to left shunt. The atrial septal defect may be readily shown by angiocardiography, but differentiation among the others in this group is difficult, and in general the method is disappointing. The Eisenmenger group includes: (a) ventricular septal defect with normal aortic root but right to left shunt due to pulmonary hypertension; and (b) the true Eisenmenger complex, ventricular septal defect with overriding aorta. These two can be differentiated only by autopsy. It is sometimes not possible to distinguish this Eisenmenger group from tetralogy of Fallot by angiocardiography, and in these cardiac catheterization is necessary.

3. Angiocardiography is usually an essential in satisfactory investigation of complete transposition of the great vessels.

4. Pure pulmonary stenosis, that is, with a normal aortic root, when studied by angiocardiography, permits visualization of the type and site of stenosis. This is in contrast to the situation when there is a tetralogy of Fallot, where the character of the stenosis can rarely be shown. The angiocardiogram permits differentiation of tetralogy of Fallot from pure pulmonary stenosis with interatrial communication quite satisfactorily.

5. Pulmonary atresia includes the anomalies in which the blood supply reaches the lungs largely or entirely from the aorta. In most of the cases examined absence of a demonstrable pulmonary artery in combination with the distinctive pulmonary vascular pattern suggesting a primary bronchial arterial supply to the lung permitted a diagnosis of pulmonary atresia. However, operation in these cases is only occasionally justified.

6. Anomalies of the tricuspid valve include atresia and Ebstein's syndrome. Atresia can usually be satisfactorily diagnosed clinically, but angiocardiography gives valuable anatomical information, confirms the diagnosis and indicates whether or not surgical correction may be carried out. If there is a pulmonary artery and the lungs are underfilled, surgery is likely to be beneficial.

Ebstein's anomaly consists of maldevelopment of the tricuspid valve with displacement of the valve into the right ventricle. This leads to gross right auricular enlargement and interferes with free flow

of blood into the pulmonary artery and lungs. An interatrial communication is often present.

Angiocardiography is usually diagnostic in these cases.

7. Coarctation of the aorta is usually localized, but the occasionally encountered extensive lesions of this type are sometimes not amenable to surgery, and in this type accurate angiocardiographic diagnosis is essential. Venous angiocardiography usually gives the information needed, but aortography yields more detailed and accurate information.

8. Uncomplicated atrial septal defects are usually satisfactorily studied clinically, and if further information is needed, catheterization is probably the method of choice. When there are other anomalies associated with the septal defect, angiocardiography is of importance.

9. In cases of patent ductus arteriosus angiocardiography probably does not add anything to the diagnosis.—*E. F. Lang, M.D.*

Gasul, Benjamin M., Weiss, Howard, Fell, Egbert, H., Dillon, Robert F., Fisher, Don L., and Marienfeld, Carl J. Angiocardiography in congenital heart disease correlated with clinical and autopsy findings; a five-year clinical and pathological study of thirty-four cases in infants and young children out of a series of eleven hundred patients, and four hundred twenty-five angiocardiograms. *A.M.A. Am. J. Dis. Child.*, April, 1953, *85*, 404–443.

This voluminous paper is a report of a study of 34 cases of congenital heart disease of which 25 were infants under one year of age. Twenty-two of the cases fell into the cyanotic group of congenital cardiac malformations. A complete clinical-pathologic correlation with angiographic studies is presented.

The authors conclude that angiography is effective in indicating intracardiac and extracardiac shunts and abnormalities in size, shape, and position of the great vessels as well as of the cardiac chambers, and in visualizing abnormalities in the return of the great veins to the heart. Its greatest contribution is in the cyanotic group of malformations. Particularly in the young cyanotic infants, whose roentgenographic and electrocardiographic evidence may be difficult to interpret and in whom cardiac catheterization may be difficult or impossible, angiocardiography is most useful.

It is of less value in the noncyanotic group of malformations as left-to-right shunts are difficult to localize accurately. However, coarctation of the aorta is a noncyanotic condition which is effectively visualized. The authors believe that angiocardiography was actually misleading in certain cases. They, therefore, warn against making a completely independent angiocardiographic diagnosis and emphasize that care must be taken in diagnosis which should be made after correlation of the angiocardiographic findings with the clinical findings. Angiocardiography must be viewed as merely another laboratory aid which is to be correlated with the history, physical examination, electrocardiography, roentgenography and fluoroscopy and cardiac catheterization, in order to arrive at a final and more complete diagnosis. From an academic standpoint it is also of great value in furthering the understanding of the abnormal hemodynamics of congenital malformations during life.

The various lesions are dealt with in detail in the paper and roentgenographic reproductions are presented in discussion of the different lesions.—*Ralph S. Bromer, M.D.*

Santy, P., Papillon, J., and Sournia, J. C. Le diagnostic angiopneumographique des opacités arrondies du poumon. (Angiopneumographic diagnosis of rounded opacities of the lung.) *J. de radiol. et d'électrol. & Arch. d'électric. méd.*, 1953, *34*, 12–17.

Neuhoff, Sussman and Nabatoff in 1949 published an important article in *Surgery* (see Abstr. this Journal, 1950, *63*, 452) dealing with the value of angiopneumography in the diagnosis of pulmonary neoplasms and established certain definite criteria of differentiation from other lesions.

With the aim of re-evaluating these criteria, the authors in the present article report brief case résumés of 15 patients with intraparenchymatous rounded opacities of the lung in whom complementary angiopneumographic examination was done prior to thoracotomy to establish a more precise diagnosis. The angiographic findings were compared in every case with the operative findings.

In 10 patients the angiographic diagnosis encountered no difficulty and supported the clinical diagnosis which was confirmed at operation. In 3 other patients the angiographic diagnosis differed from the clinical diagnosis and at operation it was found to be the correct one. In the remaining 2 patients with small shadows in the periphery of the lung, the angiographic findings suggested the presence of inflammatory lesions, whereas surgery disclosed early carcinomas of the lung, one of which was encapsulated.

The authors state that the conclusions which may be derived from a study of these cases apply only to rounded intraparenchymatous opacities of limited size and situated in the mid-portion of the lung. They are as follows: (1) common or tuberculous inflammatory lesions fail to produce arterial amputation or any other significant vascular modification; (2) stenosis or occlusion of an arterial branch of the third or fourth order is pathognomonic of a primary malignant neoplasm of a rapidly growing and in-

filtrating type; (3) benign tumors displace, deform or spread apart the pulmonary arterioles without interrupting the continuity of the vascular shadows or altering the pattern of vascularization of the surrounding structures; however, similar changes are also observed in certain slow-growing metastases. In opacities of larger size and situated near the hilar region or at the periphery of the lung, the angiopneumographic diagnosis poses entirely different problems. These are briefly discussed.—*T. Leucutia, M.D.*

DeLOACH, JAMES F., and HAYNES, JAMES W. Secondary tumors of heart and pericardium; review of the subject and report of one hundred thirty-seven cases. *A.M.A. Arch. Int. Med.*, Feb., 1953, *91*, 224–249.

The authors review the literature on secondary tumors of the heart and pericardium and report an additional 137 cases from a study of 2,547 consecutive cases autopsied at the Walter Reed Army Hospital during an eleven year period ending in 1951, including 980 cases of malignant disease. The over-all incidence of metastatic tumors of the heart and pericardium was 5.3 per cent and the incidence in the cases of malignant disease was 13.9 per cent. This latter figure is the highest thus far reported and represents only the microscopically proved secondary tumors of the heart and pericardium. The authors state that the relatively high incidence in this series is not easily explained and point out that the comparative youth of the majority of their patients who had been in military service and the marked preponderance of the male sex might have been contributory factors.

The authors note that the heart and pericardium are subject to metastatic spread from almost any primary malignant tumor and have listed numerous sources of the metastatic spread in their series. It is of interest that cardiac involvement by metastases is usually multiple and part of a general dissemination of the primary tumor, and that solitary metastasis to the heart is an extremely rare finding. In the entire series of 137 cases all but 1 case had associated intrathoracic malignancy.

Pathologically it was found that secondary tumors of the heart and pericardium usually reflect the histopathologic appearaace of the primary tumor and vary greatly in size, shape and distribution, ranging from small nodulations to large masses almost completely filling the heart chambers. Pericardial effusion was a not uncommon finding in those patients having pericardial involvement. The effusion was usually hemorrhagic. It was also noted that the right side of the heart was more frequently the site of metastases than the left.

The authors discuss some of the clinical observations in patients with secondary metastatic deposits and call attention to the following findings: development of congestive failure that is refractive to accepted therapy, dyspnea, arrhythmia, cardiomegaly, simple or hemorrhagic pericardial effusion, distant heart sounds, signs of superior vena cava obstruction, inexplicable tachycardia, pericardial friction rub or other evidence of constrictive pericarditis, roentgenologic evidence of an irregular or unusual heart border, and relative immobility of the right border of the heart on fluoroscopy. These findings should arouse suspicion of cardiac metastasis if the more common causes for these signs and symptoms can be reasonably excluded.

Treatment is briefly mentioned and consists primarily of palliation of pain and discomfort.

Of the 137 cases, 5 are discussed in detail, including clinical, laboratory and necropsy findings.—*Moris Horwitz, M.D.*

WEISBERGER, AUSTIN S., and DUMM, ROBERT M. Involvement of bone marrow in diffuse pulmonary disease. *A.M.A. Arch. Int. Med.*, Feb., 1953, *91*, 212–223.

Differential diagnosis of discrete miliary opacities or diffusely distributed pulmonary lesions, including miliary tuberculosis, sarcoidosis, fungus disease, pneumoconiosis and many other diseases is discussed by the authors. Miliary disease of the lung is frequently associated with disseminated disease and extensive laboratory studies frequently fail to establish a diagnosis. Since lymph node biopsy was frequently not feasible, the authors resorted to sternal marrow puncture.

Twenty-four consecutive patients with roentgenographic evidence of miliary opacities, or diffuse pulmonary lesions, for most of whom no diagnosis had been established, were studied by sternal marrow aspirations; similar studies were made on 25 consecutive patients with far advanced pulmonary tuberculosis. The marrow particles were prepared and studied as histologic sections. Subsequent confirmation or establishment of the diagnosis by other means was made whenever possible.

Nine of the patients with roentgenographic evidence of diffuse pulmonary disease showed a pathologic lesion in the marrow; 15 were normal histologically. Eight of the 9 with findings were diagnosable as granulomas; of the 15 cases without pathologic findings, subsequent examination showed 5 to have nondisseminated disease and 3 others have thus far not been diagnosed. The 25 patients with far advanced pulmonary tuberculosis showed no pathological findings of the bone marrow.

The authors, therefore, conclude that sternal marrow puncture is a valuable adjunct to the diagnosis of miliary disease of the lungs, representing a disseminated pathological process.—*Moris Horwitz, M.D.*

Abdomen

Jungmann, H., and Venning, P. Radiological observations of stomach changes accompanying the threat of an injection, and further data on the normal variation of peristaltic rate. *Brit. J. Radiol.*, Feb., 1953, *26*, 93–98.

A series of patients was observed fluoroscopically after administration of a barium meal for determination of the frequency and amplitude of peristaltic activity of the stomach. Subsequently, volunteers were observed during and after response to an unexpected gunshot, and during the threat of a subcutaneous injection as well as during and after the actual injection.

In 78 subjects, mainly young adults, the mean interval of peristaltic waves was about twenty seconds with a standard deviation of about 2.5 seconds. The extreme range was between fifteen and thirty seconds. When the subjects were threatened for two minutes with an injection, reduction of amplitude or total inhibition occurred in one-half of them, while in the other half there was no change. No further change was noted during the actual injection except in 5 cases (of 23 in which change was observed during the threat). These 5 fainted during the injection, and in each diminution in amplitude and finally cessation of peristalsis preceded syncope.

In the case of the unexpected gunshot, some change was noted in 65 per cent of the volunteers, but the greater number of these exhibited complete cessation of peristalsis in contrast to the response to the injection threat. An additional and more striking difference is the more rapid recovery from the gunshot stimulus.

Some volunteers stated that they soon realized that the gunshot was part of an experiment and not a cause for alarm, while the anxiety about the imminent injection persisted until the actual injection. It seems reasonable to relate the difference in the duration of inhibition to the difference in the duration of the sense of anxiety produced by these two procedures. It was also noted that anxiety or indifference, as reported later by the volunteers, was not correlated with the actual observations on the effect on the stomach; and, although some boasted of indifference, there was peristaltic change, while none was seen in some who professed anxiety.—*E. F. Lang, M.D.*

Paltrinieri, G. Il prolasso della mucosa gastrica attraverso il piloro. (Prolapse of the gastric mucosa through the pylorus.) *Ann. radiol. diag.*, 1952–1953, *25*, 245–259.

The scarcity of this subject in the Italian literature is reported by the author and many references found in the American Literature are cited. The etiology, pathology and symptomatology of this disease are discussed. The roentgen findings aiding in the diagnosis are described in detail.

The author found an incidence of 16 per cent of prolapse of the gastric mucosa through the pylorus in a series of 1,043 examinations (or 17 cases) which constitutes the basis of this report. A higher incidence was noted in women than in men in the ratio of 2:1. The diseases to be considered in the differential diagnosis are duodenal and pyloric ulcers, hypertrophic pyloric stenosis in the adult, benign prepyloric tumors, gastric polyps, duodenal polyps and papilloma, chronic hypertrophic gastritis and antral carcinoma.

Conservative medical management results in improvement in the majority of these cases which may even show reversal to normal roentgenographic findings. Surgery may be necessary in cases of intractable pain, gastric hemorrhage or cases with chronic pyloric obstruction. Two of the author's cases came to surgery with confirmation of the roentgen diagnosis.

This article stresses the importance played by the roentgen examination in making the diagnosis and also of excluding other pathological entities often found in this part of the gastrointestinal tract. Conservative medical management in the majority of cases is sufficient to control the symptoms.—*Peter E. Russo, M.D.*

Rappaport, Emanuel M., Alper, Abe, and Rappaport, Eugene O. Failure of surgery to relieve symptoms in prolapse of the gastric mucosa through the pylorus. *Ann. Int. Med.*, Feb., 1953, *38*, 224–233.

The authors call attention to the fact that current literature is replete with reports concerning prolapse of the gastric mucosa through the pylorus into the duodenal cap. They note that many obscure epigastric symptoms have been thought to occur because of this prolapse. They report 4 patients with prolapse of the gastric mucosa who had surgery and who subsequently developed recurrence of their symptoms.

The authors gained the impression that prolapse of the gastric mucosa is probably not symptomatic. They stress the fact that symptoms in their patients recurred only after a lapse of six months or more, and that, therefore, follow-up studies of these patients should be made for several years before a definite conclusion can be drawn.—*R. E. Kinzer, M.D.*

Sweetnam, W. P., Shepherd, F. W., and Murphy, E. F. Congenital obstruction of the small intestine in two premature infants. *Brit. M. J.*, April 4, 1953, *1*, 765–767.

Two cases of congenital obstruction of the small intestine in premature infants, with recovery after

operation, are reported. Over half of the neonatal deaths in England and Wales are due either to prematurity or to congenital malformations. This article describes the successful treatment of 2 infants, each presenting both of these causes.

The first case was that of an infant born a month prematurely and weighing 4 pounds, 6 ounces. On the third day, vomiting of bile-stained matter started and a normal meconium stool was passed, no food residue being noted. The abdomen was distended and peristaltic waves could be seen. Roentgenograms taken with the child in various positions revealed several gas-distended loops of the small intestine with fluid levels. A laparotomy was performed eighty hours after birth. Part of the omentum was adherent to the ileum about 12 cm. from the ileocecal junction. At this point the lumen was obstructed by a short imperforate portion, or diaphragm, the ileum above being distended while distally it was collapsed. The cecum, appendix and ascending colon were normal, though empty. An anastomosis was made between the distended ileum and cecum. The short length of collapsed ileum was left as a blind diverticulum draining also into the cecum. The baby stood the surgery well and postoperative course was uneventful. At three months of age, he weighed 10 pounds, 2 ounces and was having no trouble with feeding or bowel action.

The second case was that of a baby six weeks premature, weighing 4 pounds, 4 ounces. At delivery a defect was seen in the abdominal wall through which a mass protruded. The mass could be seen to contain intestine. The baby was placed in oxygen and left undisturbed for thirty-six hours, at which time small feedings were started. Vomiting began on the fourth day and a roentgenogram revealed gaseous distention of the small intestine with a small loop of intestine caught in the exomphalos sac. The baby was operated upon ninety hours after birth. The sac was excised and the intestine returned to the abdomen. Postoperative course was smooth.

The authors stress the importance of early diagnosis and surgery. They feel that after ninety-six hours the operative mortality is practically 100 per cent even in the most capable hands.—*Leslie L. Lemak, M.D.*

MILLER, CLARK F., and CARRIER, JOHN W. The use of telepaque in cholecystography; a comparative study. *New England J. Med.*, April 23, 1953, *248*, 709–712.

Of 13 selected cases in which cholecystograms failed to give adequate visualization of the gallbladder with priodax and would therefore have been classified as demonstrating nonfunctioning gallbladders, 6 were considered normal after re-examination with telepaque. The examination with telepaque was carried out within three days of the examination with priodax. Two other cases presented clear evidence of stones that could not be conclusively shown before with priodax.

The authors conclude that the use of telepaque enabled them to make a definite roentgen diagnosis when the findings after ingestion of priodax had been either misleading or equivocal.—*James J. McCort, M.D.*

ROTHENBERG, ROBERT E. Cholecystectomy and its relation to the stomach and duodenum; review of 75 cases with preoperative and postoperative x-ray studies. *Surg., Gynec. & Obst.*, April, 1953, *96*, 420–426.

The performance of cholecystectomy frequently leads to the subsequent roentgenographic findings of duodenal distortion or ulcer in patients who displayed normal roentgenographic findings preoperatively. This occurred in 8 patients of the series.

In the cases studied, postcholecystectomy symptoms such as colic, belching, indigestion, and dyskinesia were not found to be associated with abnormal roentgenographic findings of the stomach and duodenum.—*James J. McCort, M.D.*

ALBOT, G., TOULET, J., BONNET, G. F., and MOULLART, C. La cholécystographie de face et de profil, avec étude de l'angle d'érection vésiculaire, du volume vésiculaire et du coefficient volumétrique d'évacuation; technique, intérêt, résultats pratiques. (Cholecystography, frontal and side views, with a study of the angle of erection, volume and volumetric coefficient of evacuation of the gallbladder; technique, value, practical results.) *J. belge de radiol.*, 1953, *36*, 1–16.

During cholecystography the authors systematically use frontal and right lateral views of this viscus with the patient in decubitus. They feel that this permits a more precise evaluation of the volume of the gallbladder before and after a fat meal. In this way two functions are distinguished, evacuation measured by a "volumetric coefficient of evacuation" and contraction measured by the "angle of erection in the lateral view." By separating these functions they feel that dyskinesia is better evaluated and that there can be distinguished the normal gallbladder, infundibulo-cystic hypertonicity, atony of the gallbladder, complete stasis as well as hypercontractility.—*M. L. Sussman, M.D.*

CLAUS, E., and BAEYENS, J. Etude cholécystographique comparée de l'acide iodopanoïque (télépaque) et de l'acide iodoalphionique. (A comparative cholecystographic study of iodopanoic acid [telepaque] and iodoalphionic acid.) *J. belge de radiol.*, 1953, *36*, 17–48.

The authors subjected 100 patients, with a five day interval, to two consecutive cholecystographic examinations, one with telepaque and the other with iodoalphionic acid.

With telepaque there is a marked reduction both in frequency and in intensity of the secondary effects. The gallbladder is denser which permits fluoroscopy. The undesirable sympathomimetic effect of iodoalphionic acid is eliminated so that a more physiologic state exists. As a result, the fat meal is more effective. Hence the chances of visualizing the biliary tract are greater.

The objections to telepaque are residues of the medium in the right colon. Small defects might be obscured by the greater density but this can be obviated by modifying the technique.—*M. L. Sussman, M.D.*

Ghysens, E. La technique de la cholécystographie. (Technique of cholecystography.) *J. belge de radiol.*, 1953, *36*, 49–68.

The author considers that in addition to horizontal films, an erect film is indispensable. This is because in some cases the opacified bile is only dense enough when it collects in the fundus; in addition, calculi may be demonstrated that are otherwise hidden and it is possible to separate the gallbladder from adjacent organs and to study the effect of compression.

The author has not found the right lateral decubitus position of Kirklin particularly useful but he does examine routinely in the Trendelenburg position. He mentions that the lateral view of Albot is useful in studying function.

Nonvisualization following oral cholecystography is always checked by intravenous examination. The author states that about one-third of the nonvisualized cases are then demonstrated; however, he emphasizes that obese patients should be given adequate dosage. He also states that giving a fatty meal to empty the gallbladder before cholecystography is of little value.—*M. L. Sussman, M.D.*

Sloan, Sol, and Freedman, Toby. Aspiration and air replacement in diagnosis and management of amebic liver abscess. *A.M.A. Arch. Int. Med.*, April, 1953, *91*, 550–555.

For the delineation of an amebic abscess, roentgenologic methods such as hepatography with thorium dioxide, injection of iodized oil into the abscess cavity, and pneumoperitoneum have for the most part fallen into disrepute. The injection of air into an amebic abscess cavity following aspiration is an innocuous procedure and serves as an aid in diagnosis and in evaluating the efficacy of therapy.

A case is presented for illustration. The patient had an atypical pneumonia-like process at the right base but appropriate management failed to improve his condition. A liver abscess was then suspected and an amebic complement-fixation test was found to be positive. Emetine was started as a therapeutic trial and as pre-aspiration treatment. Sixty-five milligrams of emetine hydrochloride was given daily for seven days and then the abscess was aspirated. About 30 cc. of thick chocolate colored fluid was aspirated without cysts, trophozoites, or bacteria being found. Chloroquine phosphate was then started, 1 gm. initially, followed by 0.5 gm. daily for a total dose of 30 gm. Concurrently, the patient received 2 gm. of aureomycin daily for thirty-four days. A second abscess aspiration was done three days after the first and 500 cc. of the same material was removed. There was some clinical improvement. A third aspiration was done and this yielded 1,500 cc. of fluid, and 200 cc. of air was introduced. Roentgenograms showed an abscess cavity measuring 16 cm. in diameter. Antiamebic therapy was continued and aspirations were performed as indicated. The air in the abscess cavity aided in demonstrating the reaccumulation of fluid and served as a guide to the efficacy of therapy. It is emphasized that treatment should be carried out for seven to ten days before an abscess is aspirated unless rupture is imminent.

If one-fifth the volume of fluid removed is replaced by air, appropriate roentgenograms will give invaluable information as to size and location of the abscess cavity and will serve as a guide to further aspiration and the efficacy of therapy. It is generally agreed that open operation should only be used in the event of secondary infection which cannot be controlled by medical measures. The mortality figures rise from 4 to 5.4 per cent when conservative therapy is used, to 22 to 43 per cent when open operation is performed.—*Robert K. Arbuckle, M.D.*

Tori, G. Hepatic venography in man. *Acta radiol.*, Feb., 1953, *39*, 89–97.

After a brief review of the various methods used by other investigators for contrast visualization of the liver, the author describes his own technique. Under fluoroscopic control he catheterizes the right auricle and then manipulates the catheter into the inferior vena cava. The catheter is passed 2 to 3 cm. below the diaphragm and rotated right or left to fill either the right or the left superior group of hepatic veins. Prior to catheterization, oxygen is injected retroperitoneally to better outline the liver.

By this method the author has studied 8 normal persons and 2 patients with disease. He illustrates the vascular pattern obtained and shows that in the 2 patients with disease the pattern was altered and definitely abnormal. He emphasizes that blotchy areas of contrast medium sometimes seen on normal studies are due to the technique of injection and represent diffusion of the material into intralobular veins and sinusoids. Following a discussion of the anatomy of the hepatic veins, he states that, theoretically, the roentgenologic study of the hepatic ven-

ous outflow will contribute to the diagnosis of all those conditions of the liver accompanied by circulatory disorders.

In summary, the author emphasizes that he does not feel justified in expressing any opinion as yet on the practical possibilities of his method. He believes that only the application of the method in a large number of pathologic cases will indicate its true value.—*William H. Smith, M.D.*

Gynecology and Obstetrics

Ponzi, E., and Leonardi, L. Sull'impiego di un nuovo mezzo di contrasto nelle isterosalpingografie. (On the use of a new contrast medium in hysterosalpingography.) *Radiol. med.*, Feb., 1953, *39*, 131–135.

The authors performed for years numerous hysterosalpingographic examinations with iodized oils (lipiodol, radiopol, etc.) at the Poliambulatorio of Parma, mainly to determine the cause of sterility. The so-called "physiologic method of Rossi" was used which consists of the injection of 10 to 15 cc. of the opaque medium under low pressure, followed by the taking of a series of roentgenograms at regular intervals.

Although this procedure as a whole proved satisfactory, certain undesirable side-effects could not be obviated. These included: (1) inflammatory reactions of the tubes and peritoneal serosa; (2) pseudogranulomas and adhesions of the peritoneum due to irritation of the opaque medium; (3) penetration of the opaque medium into a blood vessel with the risk of a possible embolus; and (4) delayed pain in the epigastric region, sometimes accompanied by an attack of fever, likewise due to the irritation of the opaque medium. Since most of the patients were public assistance cases and the examination usually was carried out in an ambulatory way, these side-effects not infrequently caused considerable inconvenience.

With the aim of devising, if possible, a procedure completely devoid of irritation, the authors recently used ioduron S as the contrast medium. This new preparation is the sodium salt of diiodo-pyridone-N-acetic acid with diethanolamine to which an anesthetic (a derivative of cinchoninic acid) is added. It forms a moderately viscous solution and is water soluble, thus absorbing rather rapidly following the injection, in contradistinction to the iodized oils which, as is known, absorb at an extremely slow rate and often lead to the formation of oil retention cysts.

The examination is done in the same manner as when employing lipoidol but only 8 to 10 cc. of the solution are injected first and a roentgenogram is made to show the size and shape of the uterine cavity. Then the injection is continued and additional roentgenograms are made after 5, 15, 30 and 60 minutes to visualize the status of the tubes in case of occlusion or to observe the slow diffusion of the opaque medium into the peritoneal cavity when the tubes are patent. Occasionally, still more of the contrast solution is injected and a pelvigram made to complete the examination.

The authors have now used ioduron S in a series of 30 cases without any inconvenience whatsoever to the patient. They therefore believe that the introduction of this new medium represents a real progress in the technique of hysterosalpingography, especially if an ambulatory examination is desired.—*T. Leucutia, M.D.*

Roland, Maxwell, Carpenter, Frederick, and Rich, Joseph. A new water-soluble opaque medium in the study of hysterograms and hysterosalpingograms; preliminary report. *Am. J. Obst. & Gynec.*, Jan., 1953, *65*, 81–87.

In presenting their observations on 50 cases examined with medopaque-H, a new water soluble contrast medium for hysterosalpingography, the authors briefly review the developments leading to present-day hysterosalpingography and hysterography.

The prerequisites of an ideal medium are considered to be: (1) proper viscosity and good contrast, (2) absence of irritation and toxicity to living tissues, and particularly the reproductive organs and (3) rapid absorbability.

In comparing lipiodol with medopaque-H, it is pointed out that the chief disadvantage of lipiodol is its poor or slow absorption. In the presence of adhesions, lipiodol residues may become encysted and remain for months or years. Inflammatory reactions and infection have been reported following the use of iodized oil.

Medopaque-H (sodium ortho-iodohippurate as contrast medium, and sodium carboxymethyl cellulose as viscosity vehicle, with added stabilizer and preservatives) meets the above mentioned prerequisites better than any other medium.

Of the 50 cases at the Infertility Clinic, Department of Gynecology of Queens General Hospital, 5 were examined for endometrial studies and 45 for tubal patency.

The technique used calls for a preliminary roentgenogram of the pelvis. The examination is performed four to six days after cessation of menstruation. A bakelite speculum is used and a Jarcho cannula filled with medopaque-H is introduced into the cervical canal.

Using a 10 cc. Luer-Lok syringe filled with medopaque-H, 2 cc. injections are made at a time. Roentgenograms are made after 2, 4 and 6 cc. have been injected. This gives gradual filling of the uterus and tubes. Carbon dioxide is introduced after 6 cc. have been injected, at a pressure not to exceed 200 mm. If films reveal the opaque medium in the peritoneal cavity, the examination is discontinued; otherwise

carbon dioxide pressure is maintained for several minutes and another roentgenogram is made.

If the tubes are not patent, the examination is repeated in two months, during which period pelvic diathermy is applied.

When the examination is made only to determine the condition of the endometrium, no carbon dioxide is used.

Good reproductions of roentgenograms of illustrative cases accompany the article.—*William H. Shehadi, M.D.*

Cox, Kenneth E., and Lamar, Robert F. Colpocleisis. *Am. J. Obst. & Gynec.*, March, 1953, *65*, 583–591.

In the 7 cases of vaginal fistulas following radiation therapy for cancer of the cervix, reported here, 2 vesicovaginal fistulas had been treated elsewhere, nine and twenty-one years previously, and these patients appeared for follow-up. Of the 5 patients with rectal fistulas, 3 had survived three years or longer, apparently cancer free. The remaining 2 had carcinoma present at the site of the fistula at the time of operation, and were considered to be in a terminal condition from the standpoint of further treatment of the cancer.

The history of of the operation of colpocleisis extends over a hundred years, and the attitude of the profession, as reflected in published articles, shows well the effect of the teachings of the expert gynoplastic surgeons of fifty years ago and the effect of the use of radiation in the treatment of cervical cancer.

Three considerations have seemed of value in the selection and management of these cases in the light of present experience. Since rehabilitation is the primary object in the management of these miserable patients, it would seem unlikely that many would submit endlessly to attempts at repair by methods that admittedly promise slightly better than an even chance of cure. More patients would be benefited if preliminary survey of the patient could promise for her a near 100 per cent cure of the fistula. In these severe cases, the vagina is at best a poorly functioning organ, due to constant contamination with urine, and foul exudates. In none of the authors' series was intercourse practiced. The operation should not be undertaken in patients whose survival time would be less than that time which would offer a reasonable evidence of cure. Counseller has suggested a minimum of three years.

The success in the surgical management of these complications depends upon the nature of the fistula, the length of survival of the patient, and the presence or absence of demonstrable cancer. In attempts at repair following radiation therapy, success or failure may depend upon the ability of the operator to estimate the damage to contiguous structures by radiation and infection, resulting in their fixation, hardening, and diminished blood supply. Colpocleisis should be considered in the management of these cases, and, the use of the operation should be extended to selected cases of terminal cancer, when it will be of merciful palliative value, if only for a short time.—*Eugene J. McDonald, M.D.*

Genitourinary System

Wilson, Hugh M. Roentgenological aspects of renal function. *Yale J. Biol. & Med.*, April, 1953, *25*, 401–404.

In a general discussion, the author points out that the roentgenographic visualization of the kidney by concentrated contrast media has advanced our evaluation of renal function and the recognition of renal disease. The findings of excretory urography now include: (1) the increase of the density of the renal shadows, (2) appearance time of the contrast medium in the collecting system, and (3) evaluation of the density of excreted urine in terms of renal function. The author states that improved urograms are possible with the new iodinated compound urokon with increased concentration present and less side reactions than those previously encountered with diodrast. He notes that better visualization of the renal shadows and the renal collecting systems are obtained by the technique of using 25 cc. of 70 per cent solution of urokon. Excellent nephrograms can be obtained during arteriography when 50 cc. of urokon is used. Opacification of the liver, spleen, and kidney suggests that most of the density is due to the contrast medium in the blood capillaries. By these immediate nephrograms the functioning renal parenchyma is seen and avascular renal cysts can be differentiated from vascular cortical neoplasms. It is felt that tubular excretion plays little or no significant role in the excretory urograms.

Two factors affect the quality of the desired anatomical detail of the renal pelvis, namely: (1) density of the contrast material and (2) distention of the collecting system by opacified urine. As the plasma level of the contrast medium is high, the author recommends controlled hydration by giving water to dehydrated patients one hour prior to the intravenous injection. This has been found to insure adequate urinary output during the period of roentgen examination.

With this technique partial ureteral compression is not necessary. The usual serial roentgenograms are taken beginning five minutes after the intravenous injection of the contrast solution.—*T. D. Allison, M.D.*

Yates, T. M. Distortion of pyelogram by extrarenal lesion: liver abscess distortion of pyelogram. *J. Urol.*, Feb., 1953, *69*, 309–314.

Pyelographic study can be used as a diagnostic aid in determining the extent and nature of renal

and extrarenal lesions. Variations of the pyelogram due to extrinsic renal lesions should be carefully studied and at times their proper significance may be evaluated.

In this article, the author refers to 3 patients who have been studied by pyelographic procedures, all of whom have shown deformities of the right kidney associated with a liver abcess. In 2 of the pyelographic studies, the right kidney was displaced downward and in the third it was displaced upward with some associated ureteropelvic obstruction. In 2 instances, the liver abcess was amebic in origin.

It is difficult to explain how a swelling of an intra-abdominal organ would affect the calyces of a kidney. The author points out that as long as the retrohepatic fossa is not obliterated by inflammatory changes, pressure on the kidney from an intrahepatic mass would not be constant enough to deform the pyelogram. When this space is obliterated and the liver and kidney become a part of one mass, then the pressure from the inflammatory mass does produce pressure defects in the calyces and pelvis of the kidney as well as some displacement of the kidney.

All the cases presented showed marked signs of infection in the right abdomen. The psoas shadow on the pyelograms was retained so that a diagnosis of perinephric abcess could be excluded.—*George W. Chamberlin, M.D.*

DETSHIVERS, CHARLES H., and AXILROD, HERBERT D. Solitary renal cysts. *J. Urol.*, Feb., 1953, *69*, 193–202.

The true solitary renal cyst is generally found in the renal cortex. Occasionally, it may be in close relationship to the renal pelvis. The cysts vary in size from minute to massive. The cyst wall is composed of fibrous tissue lined with a single layer of flat endothelium. The content consists most often of serous fluid and occasionally blood is present. The etiology of these cysts is not generally agreed upon. The symptoms associated with solitary cysts of the kidney are completely absent or in some instances may be associated with pressure upon the kidney or adjacent organs.

The 3 patients reported in this article had demonstrable pyelographic deformities indicative of an intrarenal mass. The cysts were locally excised and the postoperative pyelograms are reproduced.

Both excretory and retrograde pyelograms are recommended in the diagnosis of these lesions. The pyelograms show deformity of the calyces without obliteration and usually without deformity of the true renal pelvis. It is pointed out that these pyelographic changes are not pathognomonic but merely suggestive.—*George W. Chamberlin, M.D.*

HAMILTON, GLADEN R., GETZ, RAYMOND J., and JEROME, SHEPARD. Arteriovenous fistula of the renal vessels: case report and review of the literature. *J. Urol.*, Feb., 1953, *69*, 203–207.

This is a rare condition which has been previously reported in only 3 instances. The 3 cases which are recorded in the literature have been on the basis of aneurysm with erosion forming the arteriovenous communication. In 2 instances, there was an associated hypertension and a thrill and bruit were heard in the lumbar area. The third case in the literature showed only gross hematuria clinically. There was no cardiac decompensation, no hypertension and no bruit.

The case reported here was associated with an adenocarcinoma of the kidney in which there was erosion of the tumor through the vessels of the hilum producing an arteriovenous fistula. The blood pressure was elevated, the cardiac silhouette was enlarged and the patient had a bruit present in the left lumbar area.

The roentgenograms of the chest and the pyelogram are reproduced.—*George W. Chamberlin, M.D.*

DELL'ADAMI, G., and MENEGHINI, C. Il pneumo-addome extraperitoneale nella diagnostica dei tumori renali. (Extraperitoneal pneumography in the diagnosis of renal tumors.) *Arch. ital. urol.*, 1953, *26*, 105–122.

The authors present a study of 17 patients following presacral air injection in renal tumors; from their experience they have found that the permeability of the perirenal tissue to gas is of more significance than the alteration in shape of the kidney. The degree of fixation resulting from adhesions in renal neoplasm is classified into two types, loose and solid. They have never encountered "solid" adhesions in instances of renal cystic formations which are thick and firm as those resulting from the solid tumors even though small. Of importance, also, is the extent of the adhesions outside of the perirenal fascia. Roentgenographically, it was not possible to determine whether adhesions resulted from neoplastic infiltration per se or from reaction of the perirenal tissue to the neoplasm.

The indications and limitations of retropneumoperitoneum are stated; the necessity of an accurate examination and familiarity with the method for the purpose of obtaining a more satisfactory diagnosis is recognized. The possibilities of errors due to technique and interpretation are noted.

The authors include 10 roentgenographic illustrations among which are laminagrams.—*Lucien Pascucci, M.D.*

ROSSI, LUCIO. Il retropneumoperitoneo nello studio dell'apparato urinario. (Retropneumoperitoneum in the study of the urinary system.) *Ann. radiol. diag.*, 1952–1953, *25*, 323–406.

Retropneumoperitoneum has been used by the author in a great variety of renal diseases and by this method he has been able to obtain a more correct diagnosis than when conventional methods alone are employed. He has found it of particular value in:

A. Tumors of the kidney:
   1. Especially when the involved kidney shows impairment of function and in those cases in which retrograde studies could not be carried out because of technical difficulties.
   2. In those cases in which the intravenous or retrograde studies reveal no distortion or displacement of the calyces or pelvis.
   3. In determining whether a renal tumor is benign or malignant.
   4. To help differentiate renal tumors from polycystic kidneys, tuberculous pseudotumor, unilateral hydronephrosis, renal cysts and pararenal tumors.
   5. In the study of renal tumors in children.
   6. To furnish the surgeon with detailed information as to the size, extent, attachments and other characteristics of the renal tumor.

B. Cysts of the kidney:
   1. In which the function of the kidney is impaired and the intravenous and retrograde studies make the diagnosis doubtful.
   2. To demonstrate the degree and extent of parenchymal damage.
   3. To differentiate from pararenal cysts.

C. Polycystic kidneys:
   1. Especially in those cases of unilateral involvement.

D. Hydronephrosis.
   1. In those cases which cannot be studied by intravenous or retrograde methods.
   2. To differentiate it from renal tumors or cysts.
   3. To evaluate the extent of parenchymal damage to help determine whether conservative or radical treatment should be done.

This is an excellent article demonstrating to what advantage retropneumoperitoneum can be utilized in almost any type of renal pathology, permiting many details of the upper urinary tract to be seen which are difficult or impossible to see on conventional films. The author supplements the presacral oxygen insufflation with laminagraphy and intravenous urography as a combined procedure.

The illustrations are numerous and excellent in quality. They depict advantageously the various points emphasized in the article. A complete bibliography on this subject is also appended.—*Peter E. Russo, M.D.*

Carr, J. A. The pathology of urinary calculi: radial striation. *Brit. J. Urol.*, March, 1953, *25*, 26–32.

Five hundred urinary calculi were examined for evidence of radial striation and such evidence was found in 42 per cent of them. This striation was noted only in areas composed of uric acid, calcium oxalate, monohydrate or calcium acid phosphate dihydrate. A mucinous layer on the calculus is regarded as essential for the formation of this type of calculus. Some points on the formation and structure of these stones are elicited.

It is suggested that possibly an understanding of the pathogenesis of calculi may result in a new approach to the prevention of recurrent calculi.—*C. R. McIntire, M.D.*

Dearing, Ruth. A study of the renal tract in carcinoma of the cervix. *J. Obst. & Gynaec. Brit. Emp.*, April, 1953, *60*, 165–174.

The study reported in this article was carried out on 428 patients treated at the Newcastle Regional Cancer Organization between 1947 and 1951. Of these patients 327 were seen before the commencement of treatment. During this time a total of 750 patients have been treated, but only since February, 1949, have facilities existed for performing excretory urography on every patient admitted. The treatment of the majority of the patients has been by radium or a combination of radium and surgery. Roentgen therapy has not been used.

This excellent article contains 16 tables and 7 photographic illustrations. In one table the author lists the cases in which histologic examination of the broad ligaments was possible, correlated with the urographic findings. It is noted that the incidence of the abnormal pyelogram was twice as high in the group in which the broad ligaments were found to contain carcinomatous extension.

The author states that it is doubtful whether the clinical examination is reliable as a method of assessing the presence of carcinoma in the broad ligaments. In 57 Stage II cases with suspected clinical involvement, the error in assessment was 76 per cent. Sixty-three other cases in Stage II, in which clinical examination failed to reveal involvement, showed carcinoma on histologic examination in 4 instances, giving an error of 6.3 per cent. In 30 Stage I cases, in which all 60 broad ligaments were regarded as not involved, 2 were found to contain carcinoma on histologic examination, an error of 6.6 per cent. Thus, when all the cases with clinically negative broad ligaments are interpreted as not containing carcinoma, the over-all error is only 6.4 per cent as proved by histologic examination but, when thickenings in the broad ligament are interpreted as meaning the presence of growth, the error is as high as 76 per cent.

In concluding, the author considers separately the significance of the pre-treatment pyelogram in patients with carcinoma of the cervix and the value of the use of pyelography in the follow-up of treated cases.

1. *The pre-treatment pyelogram.* An abnormality

in the pyelogram of a patient with carcinoma of the cervix is a sign of very grave significance, almost always indicating interference with the renal tract by extensions of the growth into the broad ligament or to the pelvic lymph nodes.

Since the results with radium treatment are unsatisfactory in all types of cases when the pyelogram is abnormal, some patients might be considered for pelvic exenteration on the grounds of an abnormal pyelogram when otherwise the clinical extent of the disease would not suggest this procedure.

Systematic pre-treatment study of the urinary tract is also indicated for the purpose of obtaining pyelograms for later comparison in the follow-up of the patients.

2. *The use of the pyelogram in the follow-up of treated cases.* The use of the pyelogram in these cases is of value: (a) for the early detection of changes in the urinary tract which may result from radium necrosis; and (b) for the possible demonstration of recurrence at a stage when a few of these patients may still be suitable for extended radical surgery. It should also serve as a clear indication that any further radiation therapy is contraindicated, and lastly, it may provide a means of arriving at an earlier but definite unfavorable prognosis.—*Ralph F. Niehaus, M.D.*

SANDSTRÖM, CARL. Contrast media for the kidneys, heart and vessels, and their toxicity. *Acta radiol.*, April, 1953, *39*, 281–298.

The author gives a brief historical review of the development of contrast media for excretion urography and, subsequently, for roentgen examination of other organs, especially the heart and great vessels. The author lists the following five prerequisites which a suitable contrast medium should meet:

1. It should be so compounded as to achieve the greatest opacity to the roentgen ray.
2. It should be readily soluble in water and of the same hydrogen ion concentration as the blood.
3. It should be completely inert and free of local and general toxicity to the body.
4. It should consist preferably of a single chemically well-defined stable substance.
5. The wrapping of each tube or package should clearly state the chemical composition, give an indication of the possible side-effects and complications and their treatments, the contraindications, the guaranteed life, as well as the date of manufacture.

In cases of serious side-reactions, the author suggests that a sample from the used ampule, if available, or from another ampule of the same wrapping, should be thoroughly tested for impurities.

The patient should be made aware of the nature of the reaction and told of the necessity of informing other examiners in the future.

A report of all cases with severe toxic reactions should be published in medical journals for general information. In the event of death, a postmortem examination should be performed and the results likewise published.

The author stresses the necessity of having in the department all necessary instruments and medications to be used in an emergency.

Contraindications are oversensitiveness to iodine, high-grade allergic conditions, kidney diseases with lowered kidney functions (some authors consider N. P. N. above 40 mg. per cent, a contraindication likewise a specific gravity less than 1.015). There is no proof of the value of the tests ordinarily performed prior to an examination to determine the patient's sensitivity.

The author's article is based on 80 cases of angiographies and 9,897 of urographies.

The investigations done by the author, as well as observations made by other workers, lead to the belief that abdominal compression during excretion urography causes temporary distrubance of renal function, which may give rise to serious symptoms. The author recommends as a precautionary measure slow injection of the contrast medium (2 to 3 minutes).

Ten cubic centimeters of calcium gluconate should be injected intravenously as well as intramuscularly in cases of urticaria, edema of the eyelids, and spasms of the larynx.

In cases of low blood pressure, weak pulse and cold perspiration abdominal compression should be removed. These usually are signs of primary shock and should be treated by injection of 1.0 cc. of ephedrine.

If calcium gluconate, 10 cc. intramuscularly and intravenously, does not stop twitching and convulsions, then a soluble barbiturate should be administered intravenously.

Oxygen should be given as long as blood pressure is low in order to counteract the risk of anoxia during the period of shock.

The author recommends that the following drugs and equipment be maintained at all times in every roentgen department, as they are in his office:

Apparatus: Blood pressure gauge, cylinder of oxygen with reduction valve and rubber tube, rubber mask and rubber bag (5 liters), and a pharyngeal tube.

Drugs: (a) Blood pressure increasing drugs: amp. ephedrini 5 per cent, amp. oxedrini 6 per cent (synephrine tartr. U. S. P.); (b) Hypnotics: amp. phenemali, amp. phenobarbital (U. S. P.), amp. narcotal, Astra; (c) Calcium preparations: amp. calcii gluconatis 10 per cent and amp. calcium-Sandoz 10 per cent, 'Sandoz.'—*William H. Shehadi, M.D.*

GILG, EJNAR. The influence of diphenhydramine (benadryl) on the side-effects of diodone in urography. *Acta radiol.*, April, 1953, *39*, 299–307.

The use of diodone in intravenous urography is

often accompanied by a feeling of heat in the body and a congestion of the face. Nausea and vomiting are less frequent, while dyspnea, urticaria, rhinitis, edema of the glottis and shock are more serious but are rare. A few instances of death have been reported in the literature. In view of the generally accepted theory of hypersensitivity as a cause of most of the side-effects of diodone, it should be possible to counteract some of these complications by means of antihistaminic drugs, which are known to be especially effective in treating urticaria and vasomotor rhinitis.

The author quotes investigators who studied the effects of benadryl in doses of 50 to 300 mg. The reactions noted were dizziness, tingling of the hands and feet, drowsiness, difficulty in speech, indistinct vision, tremors, and nausea. Drowsiness was experienced after doses of 100 mg. and nausea after 200 mg. There was elevation of the blood pressure of varying degrees, depending on the dose used. The use of benadryl in hypertension and heart disease is contraindicated.

With the use of antihistaminic drugs, the side-reactions of diodone are fewer, but allergic reactions are not controlled.

The author studied a group of 296 patients with diodone and a group of 416 patients with diodone cum diphenhydramine. As a contrast medium, the latter drug is as satisfactory as the control.

Some drowsiness was noted in the second group while urticaria was essentially the same in both groups. Other side-effects were only slightly decreased. In 75 per cent of the control group, a drop in blood pressure of 10 to 15 mm. was noted. With the addition of diphenyhdramine, this was less pronounced. In neither group did the blood pressure fall to 70 mm. systolic, below which urinary excretion stops.

The author stresses the following points:

1. As a contrast medium diodone with dyphenhydramine is equal to the preparation used in the control.

2. Fewer of the minor side-effects are to be expected with the newer contrast medium than with those without antihistamines.

3. The severe reactions seen are equally frequent in both groups.

4. The antihistaminic component counteracts to some degree the fall in blood pressure, caused by diodone and without any risk to hypertensive patients.

5. The possibility of hypersensitivity to dyphenhydramine must be taken into account.—*William H. Shehadi, M.D.*

Bersack, Solomon R., and Whitaker, Thomas E., Jr. Effect of diphenhydramine (benadryl) on side-reactions in intravenous urography. *A.M.A. Arch. Int. Med.*, May, 1953, *91*, 618–625.

Iodopyracet (diodrast) is the most commonly used contrast medium for intravenous urography. Undesirable side-reactions occur, the majority of which, such as nausea, vomiting, urticaria, and sneezing are of short duration and not serious. Unfortunately, severe side-reactions are also noted. During the past years several anaphylactoid deaths have been attributed to the intravenous injection of diodrast. According to statistics reported in the literature, the fatality rate is 1 in 50,000 and severe reactions occur in about 1 out of 5,000 patients. These figures indicate that diodrast is as safe as many other drugs in our medical armamentarium.

It is believed by many, including the authors, that these side-reactions have an allergic basis. In view of the present trend of considering antihistamines as the means by which to combat allergic phenomena, carefully planned study with controls was carried out to determine the effect of administering an antihistaminic drug immediately before the injection of diodrast. Diphenhydramine was used since this preparation has an antihistaminic, antiemetic, and anesthetic action.

A dose of 20 mg. diphenhydramine hydrochloride was administered intravenously immediately before the injection of diodrast. This did not definitely eliminate the allergic type of side-reactions, although there was a suggestive amelioration, evidenced by decrease from 6 per cent in the control group to 4 per cent in the diphenhydramine group. The antiemetic action, however, diminished the incidence of nausea and vomiting from 17 per cent to 2 per cent.

Rapid injections increased and slow injections decreased these side-reactions, which depend upon the chemical drug activity and upon venospasm. Side-reactions of the allergic category were more frequent in patients with a definite allergic background.

The authors believe that the results of this study do not warrant the routine administration of diphenhydramine in conjunction with the use of iodopyracet in intravenous urography.—*William H. Shehadi, M.D.*

Nervous System

Symonds, Charles. The interrelation of trauma and cervical spondylosis in compression of the cervical cord. *Lancet*, March 7, 1953, *1*, 451–454.

It appears that in certain patients without antecedent injury to the head or neck, the spinal cord is gradually compressed by the protrusion into the vertebral canal of transverse bars or ridges between the bodies of the cervical vertebrae. In other cases, cervical spondylosis follows injury to the cervical spine after a long interval, the injury being probably the initial cause of a continuing degenerative and reactive process. In a third group, the compression of the spinal cord follows injury immediately,

but roentgenograms show cervical spondylosis at the appropriate level which must have been present before the injury.

The mechanism of injuries to the spinal cord, along with the role of accidental injury added to cervical spondylosis and the appearance of sudden paralysis in cervical spondylosis without injury, is discussed.

Two cases are reported of sudden paralysis in elderly patients, without injury in the presence of severe cervical spondylosis. The suggestion is made that compression of the cord may occur from this cause in the course of normal movement. It is known that injury to the cervical spine occasionally follows manipulation of the head and neck during operation under general anesthesia with or without pre-existing cervical spondylosis. Two additional cases are presented of quadriplegia following tonsillectomy, with proof in one case of compression of the cord by a prolapsed intervertebral disc. A case is discussed in which a lesion of a cervical root immediately followed dental extraction under anesthesia in a patient with pre-existing cervical spondylosis.

From a study of the literature and the material here presented, the conclusion may be drawn that accidents involving either flexion or hyperextension of the cervical spine may cause injury to an intervertebral disc without fracture or dislocation. This may happen when the disc is normal, but is more likely to occur, especially in hyperextension, when there is cervical spondylosis with disc degeneration. In the presence of cervical spondylosis sudden compression of the spinal cord may take place with no more cause than what may be regarded as a normal effort or change of posture. The author has recognized for some time that compression of the cervical, lumbar or first sacral nerve roots and more rarely of the cauda equina may occur suddenly from disc protrusion without trauma in the ordinary sense. A word of caution is sounded to anesthetists and surgeons regarding the manipulation of the head and neck, especially in patients over thirty years of age. —*Robert D. Moreton, M.D.*

Seaman, William B., Marder, Sumner N., and Rosenbaum, Herbert E. The myelographic appearance of adhesive spinal arachnoiditis. *J. Neurosurg.*, March, 1953, *10*, 145–153.

The authors report the myelographic appearance of 7 surgically proved cases of adhesive spinal arachnoiditis. The myelographic changes produced by chronic adhesive arachnoiditis consist of complete or partial block, formation of pockets and filling defects, and spreading out of opaque oil in the form of streaks and droplets.

They conclude that because of the occurrence of complete obstruction and filling defects, differentiation from intra- and extradural tumors is difficult. They feel that an irregular ragged margin of the opaque column at the site of obstruction favors the diagnosis of arachnoiditis.—*C. Peter Truog, M.D.*

Skeletal System

Taylor, A. R. Mechanism and treatment of spinal-cord disorders associated with cervical spondylosis. *Lancet*, April 11, 1953, *1*, 717–720.

The author reviews briefly the association of spinal cord disorders with cervical spondylosis. He feels that there has never been a satisfactory explanation of how a syndrome commonly associated with compression of the spinal cord is produced without apparent compression of the cord visible at operation or postmortem.

In this article an attempt is made to show that in cervical spondylosis the spinal cord is compressed not by the disc protrusions alone, but also by the ligamenta flava, which move forward as the neck is extended.

It has previously been demonstrated that, when the neck is hyperextended, the ligamenta flava are compressed between the adjacent laminae to form bulges which project forward into the spinal canal. Myelographic reproductions are included with the neck in neutral position and hyperextended. In the latter case, the ligament projects about a third of the way across the canal. In a normal person this is of no importance; but if there is a protrusion on the anterior wall, the cord will be compressed when the neck is extended. Two other myelographic reproductions show a column of oil compressed in this way in a cadaver and a complete interruption of the column in a living person.

Treatment consists of surgery, if the patients are physically fit. The appropriate laminae and ligamenta flava are removed. If nerve roots are compressed against articular facets, the borders of these are trimmed to widen the canals. The dura is opened and any adhesions between the cord and the dura are divided so that the cord may move freely.—*Leslie L. Lemak, M.D.*

Burdeaux, Billie Dee, Jr., and Hutchison, William J. Etiology of traumatic osteoporosis. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 479–488.

After observation of distal osteoporosis in many new fractures, it occurred to the authors of this paper that stasis might possibly be the cause. Venous stasis is produced distal to the fracture by interruption of the medullary vessels, the formation of a hematoma and edema from soft tissue which retards venous return. If stasis produces bone absorption, this would be the most marked in the distal fragment.

Experiments were then done to determine whether or not venous stasis produces osteoporosis and to

compare this type of osteoporosis, if produced, with that of disuse and trauma. They concluded after study of their experimental results that the osteoporosis which rapidly appears distal to a fracture is largely due to stasis. They believe that disuse plays little part in the production of this osteoporosis for the following reasons: roentgenographic evidence of disuse osteoporosis is seen only after many months of immobilization, as they showed both experimentally and clinically. The intensity of bone absorption is too great to be due to disuse. Even after a year or more of disuse there is seldom the degree of bone absorption seen in a few weeks after a fracture. The character of acute osteoporosis following trauma differs from that of disuse osteoporosis in that the former is irregular and involves predominantly the portion of bone distal to the trauma. Osteoporosis of disuse is homogeneous and diffuse involving proximal and distal portions alike.—*Ralph S. Bromer, M.D.*

Stack, James K., and Newman, William. Neonatal osteomyelitis. *Quart. Bull., Northwestern Univ. M. School*, 1953, *27*, 69–73.

Hematogenous osteomyelitis is still seen with reasonable frequency in the newborn, as well as in older children. Even though the streptococcus or staphylococcus is the etiological agent in newborns as well as in infants and older children, the clinical course is so different in the three age groups that it suggests different lesions.

Neonatal osteomyelitis is the most insidious type, without symptoms of sepsis, or local swelling or pain. General lassitude or feeding problems may be the only symptoms, and inactivity of the involved limb may be the only sign.

Within three to ten days, roentgenograms will show evidence of widening of the joint or edema of the soft tissues. In ten to twelve days definite bone destruction will be evident in untreated or inadequately treated cases. Soft tissue swelling is the first sign to disappear followed by replacement of absorbed bone. The periosteum may be elevated early in the disease if pus penetrates under it. The cycle of roentgenographic changes is completed in as short a period as three weeks, with some thickening of the cortex persisting.

Involved areas must be aspirated early and splinted to obviate dislocation of the joint. Early antibiotic therapy is essential to prevent gross bone destruction.—*Fay H. Squire, M.D.*

Jacobs, Julian E., and Kimmelstiel, Paul. Cystic angiomatosis of the skeletal system. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 409–420.

In this paper, the authors use the term "angiomatosis" to indicate the widespread involvement of the skeletal system. The angiomatosis is designated as "cystic" because of a conspicuous correlation between the multiple angiomas and the formation of large multilocular cysts. From their review of the literature it seems that in this respect their 2 cases are unique. They conclude that this unusual but very striking observation may lend support to the theory that simple bone cysts may be pathogenetically related to angiomatous lesions.

In the 2 cases reported there were cystlike areas of destruction in the ribs, the humeri, radii, ulnae, tibiae, femora, pelvic bones, scapulae, and skull. They quote Bucy and Capps who stated that the roentgenographic appearance varies with the type of bone. Flat bones, such as the skull, scapula, and pelvis show a sunburst trabeculation of unusual size, radiating usually from a common center and mostly from the flare of the bone. The periosteum may be considerably elevated, but is apparently not broken through. In the cylindrical bones the tumor is loculated. The cortex is usually destroyed. Roentgenograms in some other cases, however, show a peculiar soap-bubble effect extending into the periosteal zone and producing only slight bone erosion. In the authors' cases the roentgenograms of the skull did not show the sunburst appearance and from a roentgenographic standpoint the lesions appeared more like those of eosinophilic granuloma.

The two cases are described in detail. The frequency and site of skeletal angiomas, the pathology, roentgenological features, clinical features and treatment are discussed. One of the most startling findings in each of their cases was the large multilocular cysts which were encountered during biopsy. The angiomatous nature of the lesion was suspected at the time of biopsy, only after correlation with the roentgenographic findings. Cysts in angiomatosis of bone are not only similar in appearance to simple bone cysts (except for their multilocularity), but they seem to have a similar explanation basically. The authors believe that the multilocular cysts in both their cases were not lymphangiomas but that they were the sequelae to relatively small hemangiohamartomas. If the histopathological and operative observations in their 2 cases are compared, it must be concluded that most of the extensive changes seen in the roentgenograms are due to secondary cysts rather than to angiomas proper. In view of the fact that the great majority of hemangiomas of bone are not associated with cyst formation, they suggest the advisability of setting these cases apart as a separate entity.

In regard to treatment, the usual orthopedic measures for pathological fractures seem to lead to good results. Meyerding is quoted who stated that hemangioma affecting bone is moderately radiosensitive under moderate dosage. With repeated roentgen treatment at regular intervals for a number of months, the tumor gradually regresses until it has disappeared. Age might be a contraindication to roentgen therapy; in both their cases no roent-

gen therapy was given because of possible interference with bone growth.—*Ralph S. Bromer, M.D.*

TESSAROLO, GINO, and SARDI, ALESSANDRO. La tubercolosi della clavicola. (Tuberculosis of the clavicle.) *Arch. di chir., ortop. e di med.*, March–April, 1953, *18*, 85–95.

A review of the literature has revealed few reports of tuberculous localization in the clavicle, The authors briefly summarize the report of Serkin, in the American literature, who in 1936 described associated pulmonary lesions in 5 and renal lesions in 2 of a total of 30 cases. The diagnosis of this entity is dependent upon the clinical, roentgenographic, bacteriological and histological studies. Therapy is surgical with removal of the focus of bone infection.

The authors were able to add 12 cases from their material. Roentgenographically the site of involvement was at the diaphyso-epiphysial junction or in the epiphysis with or without spread to the joint. This type of involvement was seen usually in patients in the 3rd decade. In infants and through the 2nd decade, a purely diaphysial process (spina ventosa) can occur though somewhat rarely. The type most easily demonstrated is a metaphysial involvement during the period of maximum bone growth and function. Later, it would seem to the authors, that in the adult, both young and old, the pathology may involve the joint and manifest itself as destruction or simple inflammatory change so limited as to be not apparent or demonstrable.

The authors presume that the major incidence in young adult males would support trauma as an etiological factor, but this was not borne out from the case histories. In 4 of their patients there was an associated exudative pleural or parenchymal pulmonary lesion. Notable was the fact that almost always the disease was homolateral.

The diagnosis does not present insurmountable difficulties. The history, diaphysial location, the roentgenographic appearance (intense reaction, extent of bone involved, ease of formation of relatively large sequestra) are important differential criteria.

Attention is called to the fact that the site of pain may be misleading. Referred shoulder pain may be present from a process at the sternal end of the clavicle.

In the discussion of treatment, the authors feel that surgery is generally indicated only in the presence of fistulas which may be present as long as eighteen to twenty-four months before bone involvement occurs.—*Lucien Pascucci, M.D.*

SHOUL, MELVIN I., and RITVO, MAX. Roentgenologic and clinical aspects of hyperphalangism (polyphalangism) and brachydactylism; hereditary abnormal segmentation of the hand. *New England J. Med.*, Feb. 12, 1953, *248*, 274–278.

A syndrome characterized by the presence of more than the normal number of phalanges in the affected digit of the hands and feet is described. This unusual feature is termed hyperphalangy or polyphalangy. The syndrome for which no definitive or etiologic name has been applied is rare. Only 40 cases have been recorded in the literature since it was described in 1896.

The five essential anatomic features are: (1) hyperphalangism, with an additional phalanx in the middle finger and sometimes the index finger; (2) brachyphalangism or shortening of certain phalanges of the hands or toes; (3) unusual length of the proximal phalanx of the ring finger; (4) an oblique and ulnarward articulation of the base of the proximal phalanx of the index finger with the corresponding metacarpal head, and (5) in preadolescent patients, the presence of a triangular bone at the base of the index finger.

The etiology of this group of anatomic abnormalities is unknown. A familial tendency has been observed and strongly suggests that the anomaly is inherited along mendelian-dominant lines.

Clinically, although the deformity is obvious, there is no interference with function. Roentgenologically the supernumerary bones should not be confused with old ununited fractures or synostoses.

There cases of this unusual anatomic abnormality are reported in detail.—*Gerald Lavner, M.D.*

BOSWORTH, DAVID M., WRIGHT, HOWARD A., FIELDING, J. WILLIAM, and GOODRICH, E. RAYMOND. A study in the use of bank bone for spine fusion in tuberculosis. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 329–332.

This paper is a report of the study of a series of 21 patients who were operated upon in an attempt to secure arthrodesis of the spine. On each patient fusion was done, bank bone being used and, on a separate occasion, fusion with the use of fresh autogenous bone. A total of seventy-one fusion procedures were performed on these 21 patients. Of these seventy-one procedures, twenty-six were done with bank bone and forty-five with fresh autogenous bone. In some the initial fusion procedure was done with autogenous bone.

The authors conclude that the pseudarthrosis rate, as calculated by vertebral interspaces covered, was almost three times as high with bank bone as with autogenous fresh bone. In repair of pseudarthroses, the failure rate of bank bone was three times that of fresh autogenous bone. The fact that bank-bone implantation gave no higher rate of pseudarthrosis they believe to be due to the accompanying meticulous Hibbs type of fusion. Bilateral spine fusion as compared with hemifusion gave no statistical advantage.—*Ralph S. Bromer, M.D.*

Hamsa, W. R., and Campbell, L. S. Giant-cell tumor of the spine; report of two cases. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 476–478.

The authors considered the presentation of the 2 cases of giant-cell tumor localized in the spine justifiable as they illustrated the value of a combination of roentgen-ray and surgical treatment. The one case occurred definitely before adolescence and therefore prior to epiphyseal closure in the vertebral body, and the other occurred late in adolescence.

The first patient was a child of six years. She was treated by roentgen therapy at that age. The dose was 1,200 r given through two oblique posterior ports with an attempt to shield the ovaries. The roentgen examination had revealed a destructive lesion in the right half of the first sacral vertebra extending into the wing of the ilium. The body of the fifth lumbar vertebra was tilted into an area of destruction in the first sacral vertebra. Roentgen examination after treatment showed improved bone detail at the tumor site. The patient was also treated by fixation for three months in a body cast. However, a marked scoliosis gradually developed because of further tilting of the fifth lumbar vertebra into the original tumor site. In retrospect, the authors note that the period of non-weight-bearing and cast fixation was probably of too short duration.

The second case was that of a fourteen year old girl whose roentgen examination revealed a destructive lesion in the left half of the twelfth dorsal vertebra, with smooth edges and some new bone formation lateral to the spine in the margins of the soft tissue enlargement felt on clinical examination. The patient was treated by roentgen therapy with a dose of 1,500 r and a corrective body cast. A spine fusion was later performed which extended from the tenth thoracic to the second lumbar vertebra with iliac bone graft reinforcement. Roentgen examination ten years later, showed that the alignment of the spine had been retained.

The authors believe that early fusion is advisable. —*Ralph S. Bromer, M.D.*

Fisher, Richard H. Multiple lesions of bone in Letterer-Siwe's disease; report of a case with culture of paracolon Arizona from bone lesions and blood, followed by response to therapy. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 445–464.

An unusual case of clinical Letterer-Siwe's disease is reported in which the author had an opportunity to investigate the development and the manner of healing of bone lesions characteristic of Letterer-Siwe's disease. The case revealed what appears to be the causative organism. The patient presented roentgenographic evidence of multiple destructive and productive lesions of the long bones, skull, and ribs, associated with generalized lymphadenopathy, fever, rapid pulse, anemia, and slightly depressed white blood cell count. The condition followed a progressive course which in eight months brought the patient close to death with a clinical syndrome which seemed most compatible with Letterer-Siwe's disease.

Over a period of a year, six different surgical biopsies were done, each from a previously untouched bone lesion. Three of the biopsies were done during the active stage of the disease, while the other 3 were made during the healing stage. The original biopsy showed nonlipid histiocytosis compatible with Letterer-Siwe's disease. The second biopsy showed the development of a lipid histiocystosis. The blood culture and tissue cultures revealed paracolon bacilli of the Arizona group.

The case is reported in detail with roentgenographic reproductions of the bone lesions. All features of the disease receded immediately following antibiotic therapy and no organisms could be isolated in repeated cultures following the remission.

The authors conclude that sufficient evidence was obtained to discard the popular concept that Letterer-Siwe's disease is necessarily fatal and that the course cannot be changed by therapy. The case strongly supports the concept of an inflammatory basis of the group of diseases in which Letterer-Siwe's disease is usually included, the etiological agent in his particular case being the paracolon bacterium of the Arizona group. The serial biopsies indicate that Letterer-Siwe's disease and Hand-Christian-Schüller disease are one disease, each representing a different histopathological phase.

Even in the absence of a positive bacterial culture in a similar case, the author advocates combined antibiotic treatment. The best antibiotics are probably chloromycetin and terramycin. Since the clinical course did not change in 4 patients treated with penicillin, he feels that this is the least effective antibiotic for organisms likely to cause the condition. He states that one should be careful in giving a prognosis in infants and children who have lesions with the criteria of "eosinophilic granuloma" since multiple lesions and different patterns may subsequently develop. The criteria of Jaffe and Lichtenstein in regard to the use of the term "eosinophilic granuloma" should be emphasized; the tendency to record any case with eosinophilia as a case of eosinophilic granuloma should be avoided.—*Ralph S. Bromer, M.D.*

Turek, Samuel L. Sarcoid disease of bone at the ankle joint. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 465–468.

Sarcoid involvement of a joint is unusual. The disease shows a predilection for the short bones of the hands and the feet, with less frequent involvement of the carpus, tarsus, long bones and the vertebrae.

Roentgenograms of the right ankle in the patient reported by the author, made at intervals during his earlier treatment, revealed an arthritic spur on the anterior lip of the tibia and diffuse osteoporosis of the ankle and of all the bones of the foot. Later examinations showed spotty atrophy of all bones about the ankle joint and tarsal region; the cystic changes noted were most marked about the tibiofibular interval and on the joint aspect of the medial malleolus. These clear circular lesions exhibited very little reactive bone and appeared to penetrate the joint. The joint space was of normal width as compared with the opposite joint. The bone trabeculae distal and proximal to the joint were diffusely thinned. A small bony outgrowth, somewhat cauliflower-like, on the posterior aspect of the talus, was also noted in the opposite talus. Chest roentgenograms and the Mantoux test were negative.

Two types of the disease are recognized. The circumscribed type is characterized by cystic areas of rarefaction in the medullary canal, with little or no reactive sclerosis. The diffuse type produces a fine reticulated pattern involving large portions of the bone, and is usually associated with broadening of the shaft and thinning of the cortex.

The clinical course of the disease is quite prolonged, but is usually benign. Diagnosis may be difficult. Sarcoidosis should be kept in mind in any low grade process such as was shown in the author's case. The findings in his case would seem to indicate that the disease process does not involve the articular cartilage. This should be helpful in differentiating it from tuberculosis. The joint changes seemed to be degenerative in origin, similar to those seen in mechanical derangements. Arthrodesis in a weight-bearing joint such as the ankle would seem to be the only way of relieving pain satisfactorily.—*Ralph S. Bromer, M.D.*

WANG, C. C., and SCHULZ, MILFORD D. Ewing's sarcoma; a study of fifty cases treated at the Massachusetts General Hospital, 1930–1952 inclusive. *New England J. Med.*, April 2, 1953, *248*, 571–576.

The authors present and discuss 50 cases of Ewing's sarcoma treated between 1930 and 1952. The symptoms, age incidence, location of the neoplasms and duration of symptoms prior to treatment were found to be in general agreement with those of previous reports in the literature.

In the group of 10 patients subjected to radical surgery, 1 was living without disease six years later when lost to follow-up. The others died of Ewing's sarcoma at varying intervals of from four to forty-eight months after surgery.

Four patients received postoperative irradiation and all of these died within six months.

Twenty-two cases received roentgen treatment alone, usually supervoltage therapy (1,200 to 2,000 kv.) with a daily tumor dose of 150–200 r, up to a total tumor dose of 6,000 r. Four of this group have survived five years or more and 3 are still surviving after shorter periods. Case studies are presented to demonstrate that sensitivity to radiation varies considerably and that the exact dosage required to destroy Ewing's sarcoma has not been established.

Palliative irradiation was administered to 14 patients. These all died of the primary disease in a period of from two months to seven years but the irradiation afforded the patients considerable subjective relief.

The authors conclude from these studies that irradiation is the treatment of choice for Ewing's sarcoma, using wide fields (preferably the entire extent of the involved bone), giving 200–300 r in air daily for a total tumor dose of 4,000–5,000 r. Vigorous palliative irradiation may give subjective relief of symptoms and perhaps prolong life.—*R. W. Emerick, M.D.*

SMITH, L. D. Hip fractures; the role of muscle contraction or intrinsic forces in the causation of fractures of the femoral neck. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 367–383.

There are three constants associated with fractures of the neck of the femur: (1) the orthostatic position of the patient just before injury; (2) the inability of the patient to move the leg after injury; (3) the usual external rotation of the affected leg. Roentgenograms of the hip show a transverse or transverse oblique fracture of the femoral neck with lesser trochanter prominent and the distal fragment displaced upward.

It seemed logical to the author to assume that, if a transverse fracture of the neck of the femur is produced by external violence in the living patient, similar fractures should be produced in human femora subjected to similar forces in the laboratory. A series of experiments were set up and carried out. One hundred and fifteen human femoral necks and hip joints were subjected to pressures and to impacts to learn why or how hips were broken through the visitation of external violence.

From the study of the author's results he assumes that cervical fractures of the femur are produced consistently by the action of the external rotator muscles of the thigh. Since external rotation of the distal fragment in this fracture is invariably present, it follows that simple internal rotation of the femur should approximate the fracture surfaces. He recommends the following steps in the reduction by manipulation of a fracture of the neck of the femur:

1. The thigh is externally rotated at the same time as moderate manual traction is applied.

2. The thigh is abducted and external rotation and traction are continued

3. The thigh in full abduction is internally rotated as manual traction is continued.

4. The thigh is adducted and internal rotation and traction are continued until the limb is parallel with the long axis of the body.

5. Internal rotation is maintained.—*Ralph S. Bromer, M.D.*

Dunlap, Knox; Shands, A. R., Jr.; Hollister, Lucius C., Jr.; Gaul, J. Stuart, Jr.; and Streit, Harold A. A new method for determination of torsion of the femur. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 289–311.

This first report on a new method of determining femoral torsion by roentgenography is concerned with (1) terminology, (2) literature, (3) description of the method, positioning of the apparatus, and interpretation of the roentgenograms, (4) description of skeletal studies to determine the accuracy of the method and sources of error, and (5) the normal and abnormal findings in the roentgenograms of the hips of 499 children and 103 adults.

The amount of torsion or twisting of the femur is determined by measuring the angle formed by the plane of the central axis of the neck with the plane of the transcondylar or fixed lower-end axis. If the plane of the femoral-neck axis points forward or anterior to the frontal plane, the angle of torsion is designated in the paper as a "plus" angle and is referred to as anteversion, antetorsion or anterior twist. If the plane of the femoral-neck axis points backward or posterior to the frontal plane, the angle is designated as a "minus" angle and is referred to as retroversion, retrotorsion or posterior twist. Most observers believe that the torsion of the femur, causing an anteversion or retroversion of the axis of the neck, occurs in the shaft and does not occur in the neck.

The authors' review of the literature is divided into three sections: (1) the methods for determination of torsion; (2) investigations on dried femora; and (3) the relationship of torsion of the femur to congenital dislocation of the hip. Numerous writers are quoted under each section.

The authors' method to determine the anatomical or true angle of torsion of the femur is summarized as follows:

1. A posteroanterior roentgenogram of the pelvis and hips is taken, and on this film the apparent angle of inclination is measured.

2. A lateral roentgenogram of the hip is taken with the lower extremity precisely positioned in a simple apparatus which has an attached radiopaque reference bar; on this film is measured the true angle of torsion.

3. The true angle of torsion is determined from the apparent angle of measured torsion and measured inclination with the use of a graph prepared from a trigonometric formula.

Sources of error when the angle of torsion is determined roentgenographically either in the skeleton or the living subject are listed as follows:

1. The amount of flexion, abduction, and rotation of the hip;

2. The angle of inclination (shaft-neck angle);

3. The angle of the roentgen ray to the film;

4. The anterior bowing of the shaft of the femur.

These sources together with the positioning of the patient are discussed in detail. Roentgenograms and graphs illustrating the method are shown and fully described.

The following studies to check the accuracy of the method and the sources of error are discussed: studies on the normal skeleton; the effect of flexion of the hip on the torsion determination in the normal skeleton; the effect of abduction of the hip on torsion determinations in the normal skeleton; the effect of anterior bowing of the femur on torsion determinations; studies on specially constructed femora to check further sources of error and to check the special trigonometric formula for the correction of the error.

Roentgenograms are reported on 1,204 hips of 499 children and 103 adults. Of these hips, 630 were in patients considered to be normal, and 574 were in patients with abnormal conditions. The abnormal conditions included congenital dislocation of the hip, coxa plana, slipped capital femoral epiphysis, fractures of the neck and trochanteric region, congenitally short lower extremities and variations of the normal anatomy of the neck.

Three additional studies of the skeleton are being carried out: one on the effect of valgus and varus of the knee on torsion; another to verify the true central axis of the acetabulum and the third to verify the reported anterior and posterior acetabular indices.—*Ralph S. Bromer, M.D.*

Ryder, Charles T., and Crane, Lawrence. Measuring femoral anteversion: the problem and a method. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 321–328.

The authors state the purpose of their paper is to describe the principles of a geometrically sound, as well as practical, roentgenographic method of measuring femoral torsion. They think that the actual technique they describe is open to improvement such as refinement in the positioning apparatus, with modifications to increase the preciseness and to reveal more surely positional errors in both roentgenograms employed in the method. The use of intra-articular radiopaque materials to define the femoral neck in the study of the very young, they believe, warrants investigation.

Four steps in the clinical application of principles for measuring femoral torsion are given as follows:

1. An anteroposterior roentgenogram is made with the femur in neutral position.

2. Another roentgenogram of the hip is made with

the hip and knee flexed 90 degrees and the thigh abducted 30 degrees.

3. Lines representing the axes of the neck and shaft are drawn on the developed anteroposterior film.

4. Lines representing the axis of the neck and the transcondylar plane are drawn on the abduction film. The two projected angles are then measured with a protractor. The true angle of anteversion is determined by reference to the graph or table which is illustrated in the paper.

The accurate locating of the axis of the femoral neck in the roentgenograms is a problem which varies with the age of the patient: before the capital epiphysis has appeared it is very difficult or impossible; in a patient nine to fifteen months of age, the reasonable sureness of the needed axis can be recognized. This can be done by bisecting the width of the neck, or the neck and the head, at two separate points and by drawing a line through the two midpoints, although usually the simple drawing of the axis "by eye" gives the same placement. The locating of the axis of the shaft on the anteroposterior film would be difficult in the presence of appreciable bowing, but the authors have not encountered this problem in the children they studied.

The other possibility of error in the use of this technique arises from inaccurate positioning of the patient when the roentgenograms are made. In the abduction view, positioning mistakes may occur from flexion, extension or rotation as well as from abduction either more or less than 30 degrees.

The authors express the hope that they and others may perfect the technique to the end that reliable information about femoral torsion in children, both normal and abnormal, may finally become available.—*Ralph S. Bromer, M.D.*

Laage, Herbert; Barnett, James C.; Brady, John M.; Dulligan, Peter J., Jr.; Fett, Herbert C., Jr.; Gallagher, Thomas F.; and Schneider, Bertram A. Horizontal lateral roentgenography of the hip in children; a preliminary report. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 387–398.

The orthodox or routine roentgenographic examination of the hip usually comprises the anteroposterior view and the lateral view made with the patient in the "frog-leg" position. This constitutes a complete examination of the head and neck of the femur only. It is not a complete examination of the hip joint, according to the authors of this paper, since the landmarks of the pelvic component are identical in each view. In the horizontal lateral view, a totally different plane of the pelvis, as well as a second plane of the head and neck, is examined. The combination of the anteroposterior and horizontal lateral views is a more complete examination of the hip joint, since this combination is in accord with the roentgenographic principle that bones and joints should be examined in at least two planes.

It has been the authors' experience that the horizontal lateral roentgenograms provide a valuable tool in the management of congenital dislocation of the hip. The view is the one in which the anteroposterior relationship of the head and acetabulum may be seen. It also has another valuable function. The angular measurement of anteversion of the neck can be calculated from this projection. They have examined other entities than congenital dislocation by means of this technique. It is their impression that anteversion of the neck of the femur is increased in Legg-Perthes disease and slipped capital femoral epiphysis.

In securing the horizontal lateral view, the authors use two simple pieces of equipment which they have found to be helpful. The first is a mount which consists of a 4 inch board mounted at a 20 degree angle. A pubic post is set in the lower end. The lower end is but 10 inches from the table top, while the upper or cephalad end is 17 inches from the table. The second piece of equipment is a slotted box designed to hold the cassette. The Lysholm grid cassette of Camp is used. The child is lifted to straddle the mount and a wide elastic-type bandage is wrapped about his trunk and the top of the board. When the pelvis is symmetrical on the mount, the pubis should abut the pubic post. The extremity on the side to be examined is elevated; with the great toe pointing at a right angle to the floor, the extremity is placed parallel with the floor. The extremity is abducted to about 20 degrees. The cassette is put on end in the holder and is placed either in the axilla or superior to the ilium. Either position is satisfactory. The roentgen-ray beam is turned in a horizontal direction and is aimed through the acetabulum at right angle to the cassette.

The paper is illustrated with roentgenograms showing the technique and the results obtained.—*Ralph S. Bromer, M.D.*

Barker, Harvey W., and Coley, Bradley L. Chordoma of lumbar vertebra. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 403–408.

Chordoma is a slow-growing malignant tumor which arises from elements of the primitive notochord. Chordomas occurring in the vertebral region are the least common, comprising less than 15 per cent of the known cases. The tumor most frequently arises in the sacrococcygeal region. The vertebral lesions involve most often the lumbar region, but all parts of the vertebral column have served as primary sites. Like chordomas elsewhere, those arising in the vertebrae are slow-growing with an insidious onset of dull pain. Pressure symptoms related to spinal nerves or the cord itself finally compel the patient to seek medical attention. Positive neurological findings due to compression of the cord or nerve-

roots may or may not be present. A palpable mass, often noted in the chordomas of the sacrococcygeal region, is seldom found.

The roentgenographic appearance of vertebral chordomas is predominantly one of bone destruction. There may, however, be an associated osteoblastic reaction. Characteristically there is involvement of adjacent vertebrae with destruction of the arch as well as of the body and collapse.

The course is slowly progressive like that of chordomas in general. Those in the vertebrae are not so prone to metastasize as those in the sacrococcygeal region, but some have been known to do so. The results of treatment of vertebral chordomas have been less encouraging than those of the sacrococcygeal region.

A case is reported in this paper of proved vertebral chordoma with palliative treatment which has been successful to date. Roentgen therapy was given over the lesion in the third lumbar vertebra, the tumor dose being 1,500 r in two weeks, using 250 kv. The therapy was continued on a million volt machine, the total tumor dose being 3,940 r, in slightly less than a month.—*Ralph S. Bromer, M.D.*

Katz, Jacob F. Congenital absence of the sacrum and coccyx. *J. Bone & Joint Surg.*, April, 1953, *35-A*, 398–402.

Agenesis of the terminal segments of the spinal column has been reported as a relatively infrequent occurrence. The failure of development may vary from mere absence of the lower coccygeal segment to complete nonexistence of the vertebrae below the tenth thoracic segment. The more extreme degrees of involvement are often incompatible with life and have been described in reports on stillbirths. The case presented in this paper is an example of absence of the spine below the fourth lumbar vertebra. This vertebra, which formed the most dependent portion of the spinal column, showed rudimentary development of its transverse processes. The iliac wings were almost entirely approximated which contributed to narrowing of the pelvis. There was a moderate left cervicothoracic and a right thoracolumbar scoliosis. Two hemivertebrae in the thoracic spine were present and there were ten ribs on the right side, corresponding to the absent halves of the vertebrae. Multiple spina bifida formations were shown in the cervical spine. The scapulae were elevated. The left foot and ankle showed equinovarus deformity.

The theories advanced have ascribed the condition to vague factors believed to produce caudal suppression by minute embryonal trauma, by varying degrees of defects in the posterior portions of the metameric segments and by "interference with a primary organizer" during the early stages of fetal development.

Despite the extensive skeletal changes, the child was able to sit and walk, although walking was materially compromised by the rigid deformity of the left foot.—*Ralph S. Bromer, M.D.*

Blood and Lymph System

Bonte, G., and Cordier, R. Phlébographie en station verticale et en série. (Phlebography in vertical position and in series.) *J. de radiol. et d'électrol. & Arch. d'électric. méd.*, 1953, *34*, 1–12.

After a discussion of the anatomy and physiology of the normal and pathologic venous circulation of the lower extremities, in which considerable attention is paid to the work of J. Cid dos Santos and to the angiokymography of Ayres de Sousa, the authors describe their own technique and present their apparatus devised for serial phlebography in vertical position.

They state that vertical phlebography is more advantageous than horizontal phlebography since (1) it is more physiologic and lends itself with greater ease to the performance of various maneuvers facilitating the demonstration of the valves, (2) it produces a more complete opacification of the venous system of the lower extremity, (3) it eliminates any artefacts due to compression of the posterior part of the thigh and calf and, if performed with the limb hanging free, even of the sole of the foot (4) it gives a more real visualization of the caliber of the veins.

The procedure is as follows: The patient is placed on the special apparatus which is a modification of the authors' apparatus used for arteriography and which permits the rapid taking of six serial roentgenograms of 15 by 100 cm. size. He is supported by sitting with his opposite ischium on a small adjustable seat fastened to the upper end of the apparatus while the foot rests on a near-by stool of suitable height. The limb to be examined hangs free in front of the cassette holder and can be rotated at will for exposures under various angles. This position also permits easy performance of the various maneuvers at the end of the examination. Before the injection a tourniquet is placed approximately 5 cm. above the tip of the internal malleolus to prevent flow of the opaque medium into the superficial venous system. A 50 per cent solution of diodone is used as the opaque medium and usually 30 cc. is injected within one and one-half minutes into a superficial vein of the foot. At the end of the injection, two roentgenograms are taken in both the anteroposterior and lateral projections, followed by other pairs at thirty to forty second intervals after which the opaque solution is "washed away" by physiologic saline. If the visualization of the veins of the thigh is also desired, roentgenograms are made of this region immediately after the injection of the physiologic solution. Owing to the large size of the films, a focus skin distance of 150 cm. is necessary, and intensifying screens of various speeds must be used to

compensate for the difference in the thickness of the thigh and leg.

The authors' technique is particularly suitable for the study of varices and ulcers of the leg, post-traumatic edema, acrocyanosis and of the sequelae of phlebitis.

The article is beautifully illustrated with reproductions of interesting phlebograms, photographs of the apparatus and diagrammatic representations of the function of the venous valves as well as of the topographic distribution of the superficial and deep veins of the lower extremity. A rich bibliography is appended.—*T. Leucutia, M.D.*

COLVIN, E. M., WALKER, J. FRANK, and SMITH, HORACE D. Ascending erect phlebography; management of chronic venous insufficiency of lower extremity. *A.M.A. Arch. Surg.*, March, 1953, *66*, 292–300.

The management of chronic venous insufficiency of the lower extremity, particularly the postphlebitic type is discussed in this paper.

A detailed description of the technique for ascending erect phlebography is given. The authors do not believe that this examination is necessary for the usual varicose veins. It is indicated, however, in cases in which there is a definite history of deep thrombophlebitis or in those in which there is any doubt concerning the status of the deep venous system.—*J. Champion, M.D.*

BOYCE, WILLIAM H., DETAR, JOHN H., and VEST, SAMUEL A. A new technique of venography of the lower extremities with urokon. *Surg., Gynec. & Obst.*, April, 1953, *96*, 471–481.

The opaque medium used in the present group of 87 patients was buffered 70 per cent urokon sodium. In males 50 cc. is injected into the superficial dorsal median vein of the penis, a size 21 or 23 gauge needle being used. The superficial dorsal vein of the penis usually drains into the saphenous veins of both sides, whereas each lateral vein of the penis empties into the ipsilateral side. Injection of the contrast medium directly into the superficial external pudendal vein, the superficial circumflex iliac or other superficial thigh veins may be necessary or desirable when the penile vein cannot be used for any reason.

Because of its relatively high specific gravity the contrast material will gravitate into the dependent veins to the point of the first competent valvular system. The main trunk of the profunda femoris vein will be visualized by this technique, a feat which cannot be consistently duplicated by any method of distal injection.—*James J. McCort, M.D.*

BEACONSFIELD, PETER, and KUNLIN, JEAN. Insidious thrombosis of the aortic bifurcation; report of thirty-five cases. *A.M.A. Arch. Surg.*, March, 1953, *66*, 356–364.

This paper discusses 35 patients with thrombosis of the aortic bifurcation seen between the years 1944–1951. In this group of cases the cause of the thrombosis was arteriosclerosis in 28, inflammatory arteritis in 3, thromboangitis in 2, syphilis in one, and trauma in one. The average age of the arteriosclerotic group was fifty-two years.

Usually one or more of the following symptoms were present: (1) Fatigue of both lower extremities; (2) pain, unilateral or bilateral, usually more of a dull ache than of intermittent claudication; (3) low back pain; (4) loss of sustained erection due to the poor blood supply of the corpus cavernosum.

On physical examination there was noted absence of arterial pulsation in both legs and pallor of both legs. In the late stages of the disease all of the findings of obliterative arterial disease were present. Except for coarctation of the aorta, the only other condition which causes similar symptoms is obliteration of both common iliac arteries.

To confirm the diagnosis an aortogram is of definite value. Aortography was performed on 31 of the 35 patients and in all a complete obliteration of the terminal aorta was demonstrated.

The treatment consists of bilateral lumbar sympathectomy to improve the circulation of the legs. This is followed by resection of the thrombosed portion of the terminal aorta and common iliac arteries.

The results were poor in the far advanced lesion. Twenty-eight patients were first seen in the early stage of the disease. Of these, 24 were treated surgically (bilateral lumbar sympathectomy) and 2 died, 1 postoperatively and 1 from renal failure. Three remained unchanged, 16 improved and 3 became symptom free.—*J. Champion, M.D.*

OUDOT, JACQUES, and BEACONSFIELD, PETER. Thrombosis of the aortic bifurcation treated by resection and homograft replacement; report of five cases. *A.M.A. Arch. Surg.*, March, 1953, *66*, 365–374.

The authors state that the ideal treatment of arterial thrombosis is replacement of the obliterated segment by means of a vascular graft. They give a detailed account of the operative technique of resection of the aortic bifurcation and replacement by homograft. The use of anticoagulants postoperatively is emphasized. Five cases are presented.—*J. S. Whitmore, M.D.*

BICHEL, JØRGEN, and BASTRUP-MADSEN, POUL. Alcohol pain in Hodgkin's disease. *Lancet*, April 18, 1953, *1*, 764–766.

The authors have studied 62 patients being treated for Hodgkin's disease at the Radium Centre, Aarhus, Denmark. Nine of these patients were found to have

an unusual symptom, consisting of pain which occurred a few minutes after the ingestion of alcohol, even in small quantities. The pain was noted following the ingestion of one glass of beer as well as after beverages of higher alcoholic content and was always localized at the site of active involvement. It occurred in enlarged lymph nodes, in the mediastinal region and in bone. When the disease had been rendered more or less inactive by roentgen therapy or chemotherapy, alcohol did not produce pain. In at least one instance, the spontaneous "alcohol pain" was one of the earliest symptoms of the disease. The authors have not found this to occur in other diseases and they have not been able to induce a similar pain by the administration of vasodilators, topical ointment, histamine hydrochloride or nicotinic acid.

Although this type of pain was found to occur in only 9 of 62 patients with Hodgkin's disease, the authors believe that the "alcohol pain" may represent a specific diagnostic test.—*C. L. Hinkel, M.D.*

Yamasowa, Yoshimichi. Hematologic studies of irradiated survivors in Hiroshima, Japan. *A.M.A. Arch. Int. Med.*, March, 1953, *91*, 310–314.

This is a report on the latest effects of radiation on the hemopoietic system of 824 survivors of the Hiroshima explosion. These were compared with 1,145 controls. The studies average three and a half years after exposure.

The conclusion is that there have been no significant variations in the hematologic findings of the survivors, when compared to the control group, which could not be accounted for by differences in inherent errors in the methods of study, or by nutritional differences or by parasitism.—*Norman Heilbrun, M.D.*

RADIATION THERAPY

Brown, W. M. Court, and Mahler, R. F. Discussion on the radiation syndrome; some clinical and biochemical observations following a single therapeutic dose of x-rays. *Proc. Roy. Soc. Med.*, April, 1953, *46*, 245–250.

It has been shown that exposure of an individual to a single dose of total body irradiation results in the general radiation syndrome. This comprises four periods: the period of initial reaction with nausea, vomiting and fatigue; the period of acute reaction with ulceration of the gastrointestinal tract, acute marrow failure, bacterial infections and epilation; the period of subacute reaction with more chronic forms of infection such as lung and brain abscesses and chronic ulceration of the bowel; and the period of chronic reaction of indefinite length with anemia and malnutrition and possibly leukemia.

The authors have studied a series of patients who have received a single therapeutic dose of roentgen radiation and have demonstrated a pattern of symptoms which is a milder version of the period of initial reaction of the general radiation syndrome. The dosage was expressed in megagram-roentgens as an index of the total amount of energy absorbed by the body. The chief sites of irradiation were the whole length of the spine, the upper half of the trunk and the abdomen. The mean dose to the first two sites was 3.9 megagram-roentgens and to the abdomen 3.3 megagram-roentgens.

The pattern of reaction consisted of a latent period, a period of acute disturbance and a period of recovery. The mean length of the latent period was two and three-quarter hours with the shortest time in the patients showing the severest reactions. The period of acute disturbance began with sudden onset of fatigue, anorexia and nausea persisting for about an hour in patients who have had only mild reaction. With more severe reaction, vomiting and retching supervened and this stage lasted for two or three hours. The recovery phase required from one to five days, depending on the severity of the disturbance. Apparently two basic mechanisms were involved since in some patients fatigue was the only symptom and in other patients nausea and vomiting were the only complaints.

Blood studies revealed no significant changes in the red blood cell counts and hemoglobin or in red cell fragility or blood heparin levels. The total white blood cell count showed an increase at the time of the onset of symptoms; the neutrophil and lymphocytic fractions began to decrease at the end of the first day or during the second day and reached a maximum depression between the seventh and twelfth day in the most severely upset patients. This time of maximum depression agreed closely with the period of acute reaction of the general radiation syndrome. There appeared to be a definite correlation between the degree of symptomatic upset and the level to which the total white blood cell count fell.

Daily studies of water and electrolyte balances carried out on a number of patients showed that a negative state of salt and water balance was frequently associated with radiation sickness and there appeared to be a correlation between the symptom of fatigue and the negative salt and water balance. Urine studies revealed that associated with the onset of symptoms there was a tendency to rise in the excretion rates of sodium, chloride and phosphorus frequently accompanied by a rise in the rate of urine flow and often a rise in urine pH. When vomiting occurred, the glomerular filtration rate, as measured by creatine, tended to fall and the electrolyte excretion rates dropped to very low levels. No consistent changes occurred in the plasma levels of sodium, chloride and phosphorus at the time of these urinary changes.—*Leslie K. Sycamore, M.D.*

Wheatley, B. M., Steed, P. R., Savage, E. W., King, J. H., Forster, E. W., Hodt, H. J., Jones, I. R., and Smithers, D. W. The two million volt Van de Graaff generator installation designed for rotation therapy at the Royal Cancer Hospital. *Brit. J. Radiol.*, Feb., 1953, *26*, 57–72.

This is a composite article dealing with the various problems encountered in the installation and operation of the 2 mev. rotation therapy plant at the Royal Cancer Hospital, London, England. The plant was formally opened for the treatment of patients by Professor John Trump, of the Massachusetts Institute of Technology, in July, 1950. The article is divided into seven sections.

I. Smithers, D. W. Introduction: General considerations.

The installation at the Royal Cancer Hospital differs from those at the Sheffield National Centre of Radiotherapy and the Westminster Hospital of London in that it provides facilities for conventional treatment fields, grid fields and a variation of rotation techniques.

The extensive structural alterations which were necessary to house the apparatus proper as well as the many accessories, such as the motor rotating the floor, the cylinder banks containing the nitrogen and carbon dioxide gas used to insulate the generator, the booster pumps for cooling the water supply to the target, the vacuum pumps of the tube, the control board, etc., are briefly described. A diagrammatic representation of the treatment room is included.

II. Wheatley, B. M., Hodt, H. J., and Savage, E. W. Beam definition, beam direction, and protection problems.

The open end of the tube contains the gold transmission target surrounded by a water jacket and is enclosed in a massive lead cone provided with two sets of blocks of G.E.C. heavy alloy (95 per cent tungsten) for defining circular fields or square and rectangular fields. There is also an arrangement for defining grid fields. These fields are used either at 67 cm. or 100 cm. focus skin distance; the largest field size is 18 by 22 cm. at 100 cm. focus distance.

To secure precise beam direction in ordinary therapy, facilities are available for adjusting and defining the field size and position, the angle of entry of the beam, the focus-skin distance and the exit point of the central ray. When rotation techniques are used, additional arrangements are necessary depending on whether the rotation is done with the patient vertical and the tube in a horizontal position or with the patient lying horizontally and the tube being angulated from above downward toward the axis of the rotation. These arrangements as well as the optical defining systems and the procedure of accurate alignment of the beam-direction apparatus are discussed and illustrated with photographs and diagrams.

The protection entailed rather unusual considerations since the installation is in the basement of a multi-storied building. A collar of heavy alloy blocks was placed around the steel section of the roentgen tube and a ring of lead was added to the already existing lead plug at the top of the pressure tank to limit the upward radiation from the target. By this means the dosage level in the rooms above the installation was reduced to approximately 30 mr per week.

III. King, J. H., Forester, E. W., and Wheatley, B. M. Engineering of the rotating floor.

In this section the authors briefly present the mechanical, electrical and timing circuit designs of the turn-table which is made of steel, measures seven feet in diameter and is mounted just clear of the floor.

The motor used for the rotation of the table is housed in a pit below the treament room and has a variable speed permitting completion of a whole revolution or any given fraction of a revolution in a predetermined time commensurate with the prescribed dose. The variation in speed is controlled by a modified form of a commercial electronic apparatus ("emotrol") and a dial records the actual rotation of the table. In all rotation techniques the control of the time of the treatment is transferred entirely to the turn-table and the current is automatically switched off when the table has made the required rotation.

IV. Wheatley, B. M. Dose distribution for single fields.

The author states that the difficulties inherent in the production and measurement of clinically useful roentgen-ray beams are at a minimum in the 2 mev. region since at this level the polar diagram of the radiation is still wide enough for a large single field (*e.g.*, 20 by 20 cm. at 100 cm.) to be uniformly irradiated, the absorption occurs mainly by the compton process, the scatter is small and almost entirely in the forward direction and the ionization peak lies several millimeters below the skin.

Central axis depth dose measurements relative to the dose at 1 cm. below the surface were carried out with the aid of a direct reading dose-rate meter having a very small ionization chamber and were found to coincide with those of other investigators. The backscatter, even with large fields, amounted to only 12 per cent. Determination of the isodose curves in a horizontal plane by means of photographic films in a wax phantom proved superior to the usual procedures by means of ionization measurements since the penumbral region associated with large focal spots was clearly demonstrated. This was found to be of the order of 1 cm. at 100 cm. focus-skin distance. According to the author, the most important effect of the large focal spot size with the present tubes is the reduction of dose rate when using small fields, especially with grids.

V. Steed, P. R. Three-dimensional dose distribution with rotation techniques.

As already mentioned, the turn-table permits rotation with the patient vertical, in which case the "axis of rotation" passes through the center of the tumor, or with the patient lying horizontally when the axis of the inclined roentgen tube passes through the center of the tumor intersecting the axis of rotation.

The author, in this section, discusses dose distributions applying mainly to horizontal rotation therapy for the computation of which a technique similar to that employed in 400 kv. rotation therapy was used. However, since photographic and water phantom measurements have shown that with 2 mev. radiation the distortion of the isodose curves due to the inclination of the beam was negligible, it was not found necessary to obtain curves in two planes at right angles to each other as was with the 400 kv. rotation therapy. This greatly simplified the calculations and permitted the use of the Mayneord contour projector, the working of which is described in detail and illustrated.

The author gives examples of dose distribution estimations for continuous 360° and 300° rotations and for horizontal rotation with irradiation from two sides (anteriorly and posteriorly) and expresses the opinion that often considerable advantage can be gained by treating from opposite sides of the volume, both areas being, of course, circular and centered to the vertical axis of rotation. He also gives a rapid method of estimating the depth of the maximum dose below the surface with the aid of the so-called "optidose charts" which contain graphs showing the distribution of radiation along the vertical axis of rotation for one given field size, for various combinations of angle and radius of rotation. The curves, which are reproduced, have been so arranged that if the depth of the tumor is known, the combination of the angle and radius of rotation giving the highest dose at that depth is easily found. Further graphs are provided from which the dose at the lateral edge of the turmor and the associated skin dose for the same treatment factors can be obtained.

Examples of distributions for vertical rotation therapy have been given in former publications.

VI. Jones, I. R. Operation and maintenance.

A running-up of the generator for thirty or forty minutes to the required current is necessary before the day's treatments. Although the output of the tube has been found to be fairly constant, a calibration with a Victoreen dose meter is advisable every morning to check this. It is very important to control the potential during treatment, since voltage changes may lead to large variations in output, influencing the contemplated dosage. A daily record must also be kept of the water pressure and insulating gas pressure.

Since the roentgen tube is continuously evacuated, proper maintenance of the vacuum system is necessary. Each morning and evening the traps are filled with solid carbon dioxide and once a month the mercury contamination of the diffusion pump is removed. This procedure is described. The target of the roentgen tube and the diffusion pumps are cooled by tap water, therefore an appropriate rate of flow of the water must be maintained.

Frequent checks are necessary to ensure that the focal spot has not shifted and that the optical aligning device is coincident with the roentgen beam.

The maintenance problems concern chiefly the operation life of the roentgen tube and of the charging belt. With the high currents of 150 to 250 microamperes used, tube life has so far not exceeded 200 hours. Belt life is considerably longer and depends to a large extent on proper tension between the upper and lower pulley.

VII. Smithers, D. W. the first two years of clinical experience with 2 MeV radiotherapy.

A series of 109 cases were treated during this period, distributed as follows: carcinoma of the bladder, 26 cases; carcinoma of the bronchus, 25 cases; tumors of the brain, 16 cases; carcinoma of the uterus, 16 cases; carcinoma of the esophagus, 4 cases; and miscellaneous malignant disease, 22 cases.

The most outstanding clinical observation so far has been the lack of general or local reaction. Thus it has been possible to administer on numerous occasions a tumor dose of as much as 7,000 r to a volume of tissue 6 cm. or more in diameter at a depth of about 8 or 9 cm. without any general reaction whatsoever and with only a faint erythema of the skin.

It is too early to attempt to express an opinion as to the merit of this form of therapy. It appears, however, that valuable palliation can be obtained in many patients with far less distress from the treatment than has been possible with any method available in the past.—*T. Leucutia, M.D.*

Wilson, C. W., and Perry, B. J. Physical observations relating to the 2 MeV Van de Graaff electrostatic generator at Westminster Hospital. *Brit. J. Radiol.*, April, 1952, *25*, 210–219.

In the fall of 1950, a 2 mev. Van de Graaff generator was installed at Westminster Hospital, London, England. In the present article the authors relate their initial experience with this type of apparatus.

The unit forms part of the equipment of the Radiotherapy Department and is housed in a room previously used for a 200 kv. therapy set. In view of the favorable general layout of the department which is situated on the lower ground floor extending well beyond the main building, only few structural alterations were necessary and the required protection was realized with ease. The patient is viewed from the control station through a water-filled window which is built into one of the walls and is lined with lead glass. After a use of ten months, the water is as clear as when first introduced.

The general performance of the apparatus has been quite good. The first tube had run for 454 hours before it needed replacement. The original belt is still in use after more than 1,000 hours.

The authors made protection studies outside the treatment room and measured the stray radiation around the generator inside the treatment room. The figures obtained are tabulated and the fall of the dose rates from the tube end toward the observation window is diagrammatically illustrated.

Other physical factors which were studied carefully include: secondary electron emission from the diaphragm system; quality of the emitted roentgen beam; initial build-up of ionization within a phantom; percentage depth dose for square and elongated fields; dose contours of beams; roentgen-ray output; and variations in beam positions.

Graphs, curves and tables are used to present the pertinent data more concisely.—*T. Leucutia, M.D.*

HOWARTH, J. L., and KING, G. M. A technique for beam direction with a 2 MeV x-ray generator. *Brit. J. Radiol.*, March, 1953, *26*, 149–151.

The authors devised a technique for beam direction which is used in connection with the 2 mev. Van de Graaff generator at the Sheffield National Centre for Radiotherapy. The new technique was necessary in order to avoid interference with the subcutaneous build-up of the ionization which is one of the advantages of the high energy radiations, accounting for the greatly reduced effect on the skin.

The purpose was accomplished in the following way: Since the roentgen beam cannot strike any solid material between the defining diaphragms and the skin and since this distance for small fields with 2 mev. radiation must be at least 20 cm., the original 200 kv. beam direction technique in which plaster shells and a back pointer are employed was modified to meet these requirements. Thus the wax seatings for the applicator ends were replaced by cast aluminum rings which are fastened to the shells with plaster bandage, the part of plaster shell inside the ring being cut away to expose the skin. An additional section has been inserted above that which carries the tungsten defining diaphragms so as to bring these 10 cm. further from the target. A cylindrical detachable perspex tube was mounted on the end of the circular field insert. This tube is 26.5 cm. long and when fixed into the seating aluminum rings permits treatment at a distance of approximately 70 cm. from the target. Circular fields of 4, 5, 6, 7 and 8 cm. diameters have been used so far but the method is equally suitable for rectangular fields.

The new device is illustrated diagrammatically and a photograph showing the patient under treatment is included. Dose distribution charts are also given for lesions of the pituitary gland, tongue and right tonsil. It was possible to administer a dose of 4,000 r in four weeks in cases of pituitary adenoma without permanent epilation and doses of 5,000 r in five weeks to various head and neck lesions without producing any visible skin reaction at the end of the treatment. The ease and accuracy of setting up the patient for treatment are as great as with the original 200 kv. beam-direction technique.—*T. Leucutia, M.D.*

LAYNE, D. A., LOGUE, VALENTINE, MAYNEORD, W. V., MCKISSOCK, WYLIE, and SMITHERS, D. W. The treatment of cerebral gliomas with 24-million-volt x rays. *Lancet*, March 14, 1953, *1*, 516–519.

This is a preliminary report dealing with the clinical experience and results obtained in 10 patients with cerebral glioma who were treated since May, 1950, at the Royal Cancer Hospital, London, England, with 24 mev. roentgen rays.

The apparatus, which is an electron-synchrotron, was described in detail elsewhere (*Nature*, 1949, *164*, 726). For clinical practice it is usually operated at a potential of 24 mev. when the output is 5 roentgens per minute at 1 meter distance. The depth dose in the tissues reaches its maximum value at 3.5 cm. Recently a new collimating system has been installed embodying kinematic mounting, optical projection devices and interlock to ensure that the correct field size is being employed. The low-frequency sound inherent to all electron-synchrotrons has also been reduced considerably, so that it no longer constitutes an annoyance to the patient.

The authors enumerate the following physical advantages of 24 mev. roentgen therapy over the 200 kv. roentgen therapy: (1) the relatively low surface effect as compared to that at a depth; (2) the relatively less differential absorption in bone as compared to that in soft tissues; and (3) the relatively less whole-body effect (integral dose) outside the direct beam, due to the natural canalization of the primary roentgen beam at such high potentials.

Experimental investigations were carried out in collaboration with Spear, of the Strangeways Research Laboratory, Cambridge, on certain biologic effects of the 24 mev. roentgen rays, as for example, on cell division in vitro, on the processes of differentiation in the chick embryo and on mouse tumors. It was found that these effects were qualitatively and quantitatively similar to those observed following exposure to a comparable but smaller dose of gamma rays. Experiments on *Drosophila* fly and bean roots gave similar results, leading to the conclusion that such therapeutic superiority as exists lies solely in the better distribution of the absorbed energy of the 24 mev. roentgen rays in the tissues, as indicated by the above enumerated physical advantages,

and not in any fundamental difference in the nature of the biologic actions.

The 10 patients with cerebral glioma were selected for treatment because of the realtively small volume of their tumors, in view of the fact that the apparatus has a low output, necessitating immobilization of the patient for an hour or more each day, and that a fixed horizontal beam of small size is used, greatly limiting the part of the body which could be accurately treated. The treatment plan consisted in the administration of a dose of 7,000 r on the tumor in seven weeks by usually employing four fields for crossfiring.

No general reaction was noted in a single case and the local reactions have been far less than with lower voltage therapy. Epilation has occurred at an energy absorption equivalent to about 1,800 to 2,000 r and a few patients developed a faint erythema.

The particulars of the patients are given in short résumés and the more important data are tabularly arranged. One patient died four months after treatment; the remaining 9 are alive, many of them well and working. Since the life expectancy of patients with cerebral gliomas not infrequently exceeds several years, it is too early as yet to express a definite opinion as to the final value of this form of therapy. As regards the immediate palliation, however, the authors have no doubt of its success or of its advantages over any other method of radiation therapy.—*T. Leucutia, M.D.*

Huggins, Charles, and Dao, Thomas L-Y. Adrenalectomy and oöphorectomy in treatment of advanced carcinoma of the breast. *J.A.M.A.*, April 18, 1953, *151*, 1388–1394.

Removal of the gonads and adrenal glands results in the reduction of physiologically active steroids.

Cancer of the breast is not a single pathological state but consists of categories that differ in clinical and functional characteristics. This is verified by the observation of different rates of growth of various mammary neoplasms in an artificially steroid-poor environment. Some of the neoplasms in both sexes are composed of cells of sufficient functional maturity that they undergo a decrease of activity when critical quantities of supporting hormones are removed surgically; the patient is benefited in this circumstance. Other mammary cancers are immature and do not respond favorably to withdrawal of steroid hormones.

Most of the cancers that were predominantly papillary or adenocarcinomas regressed after surgical procedures, duct carcinomas rarely did so and undifferentiated mammary cancers never responded favorably. Adrenalectomy alone or combined with oöphorectomy has induced significant and prolonged regression of extensive mammary cancers of women who had not responded to earlier treatment with testosterone and roentgen irradiation of the ovaries. Adrenalectomy alone has provided a remission in men and women in whom the disease was advancing despite removal of testes or ovaries.

The improvement after adrenalectomy in cancer of the female breast seems to be due to the withdrawal of critical amounts of hormones similar to those formed in the ovary. After adrenalectomy in women who have undergone oöphorectomy, the excretion of estrogens in the urine disappears. Increased pituitary activity of the type that occurs in postmenopausal women is not incompatible with regression of mammary cancer.—*Chauncey N. Borman, M.D.*

RADIOISOTOPES

Eisenbud, Merril, and Harley, John H. Radioactive dust from nuclear detonations. *Science*, Feb. 13, 1953, *117*, 141–147.

With the increased activity in atomic weapons testing have come reports of transient increases in the radioactivity level in many communities of the United States and Canada. These increases are of interest to several groups not connected directly with the Atomic Energy Commission, including scientists engaged in low-level radiation measurements, uranium prospectors, and various segments of the photographic industry. In order to assist these groups, as well as to gather scientific information, the Atomic Energy Commission has set up a monitoring program to measure the changes in radioactivity levels caused by nuclear detonations.

The monitoring system is operated through a network of fixed monitoring stations and mobile monitoring teams. They sample the settled radioactive dust at ground level and, at some locations, the concentration of dust suspended in the air. The entire monitoring program is described in detail, with charts showing the variations in fallout with distance from the test site.

The significance of these data in relation to the natural radioactive background is discussed. It is shown that for brief periods immediately following a detonation, the radioactive background can be markedly increased in some areas, but the cumulative dose from such depositions are minute because of the rapid decay of the activity. The long-lived components of the radioactivity are of a low order compared with the natural radioactivity of the earth's surface and atmosphere.—*D. S. Kellogg, M.D.*

Okita, G. T., Kelsey, F. E., Talso, P. J., Smith, L. B., and Geiling, E. M. K. Studies on the renal excretion of radioactive digitoxin in human subjects with cardiac failure. *Circulation*, Feb., 1953, *7*, 161–168.

This study was made to gain further information concerning the mode of elimination of digitoxin in

human subjects. Radioactive carbon[14]-labelled digitoxin was used in patients with cardiac insufficiency, and the renal excretion rate studied using the extremely sensitive isotope tracer technique.

Contrary to the concept held by many of the earlier investigators, the major route of excretion of digitoxin in human beings seems to be through the kidneys and not by way of the liver and gastrointestinal tract. It was found that 60 to 80 per cent was eliminated through this route either in the form of "unchanged" digitoxin or its metabolic products.

In some animals, however, the major route of digitoxin excretion seems to be through the gastrointestinal tract. It has been found that rats (digitoxin-resistant animals) excrete most of the drug through the gastrointestinal tract, while cats (digitoxin-sensitive animals) excrete it about equally between the renal and gastrointestinal systems. In the light of these facts and those of the present investigation, there is the possibility that the more sensitive an animal species is to digitoxin, the more likely it will be to excrete a larger portion of the drug through the kidneys.

In these studies there was a very marked initial excretion of digitoxin during the first two days, followed by a gradual leveling off of the excretion gradient after about the fifth day. A minute amount of "unchanged" digitoxin is detected in the urine for as long as forty days after administration of a single dose of radioacitve digitoxin, while carbon[14]-labelled compounds can be detected up to the seventy-fourth day. Most of the carbon[14] from the labelled drug is eliminated in the form of metabolic products, while only 6 to 10 per cent of the original drug is excreted as "unchanged" digitoxin.—*D. S. Kellogg, M. D.*

Brownell, Gordon L., and Stanbury, John B. Instrumentation for thyroid measurement. *J. Clin. Endocrinol. & Metabol.*, Feb., 1953, *13*, 210–220.

The authors discuss the problems arising in the measurement of radioactive iodine for the study of thyroid physiology. The problems are grouped into: absolute determination of the quantity of radioactive iodine within the thyroid gland; determination of the distribution of radioactive iodine in certain parts of the body; and the measurement of activity in biologic samples of body fluid.

A high sensitivity gamma-ray detector or a scintillation counter permits accurate readings with comparatively small doses of radioiodine. The instrument is located at a fixed distance from the surface of the neck. The chief sources of error in absolute determinations are the uncertainty of the position of the sources within the body and the effect of absorption and scattering of radiation by the tissues. The authors employ an instrument, described by Freedberg, which uses 4 detectors placed equidistantly on a circle about the neck on the patient. This instrument minimizes the effect of scattering and eliminates the necessity of determining the exact location of the source.

The effect of scattering and degradation is discussed. In practice, it is not so important to eliminate the effect as it is to make the effect independent of neck size and geometry. An average correction factor can be used as generally the variation in neck diameters is sufficiently small.

The same type of instrument is employed in determining the degree of radioactivity in other parts of the body. A lead collimator with an appropriate aperture is of definite value. The counting rate is inversely proportional to the aperture size. The authors prefer a 1 inch aperture and have inserts which decrease it to ½ inch. Another collimator has a 4 inch flare and is used for large areas. The instrument can be connected to a conventional scaler.

Urine samples can be accurately measured by placing the flask on a special platform which can be rotated to the center of the 4 counter array. Correction factors for absorption and scattering must be applied to compare with the reading of the standard. Urines that are highly radioactive can be measured in 100 cc. portions and sometimes a few centimeters in a test tube are sufficient.

The determination of radioactive iodine in plasma is quite different due to the small amounts involved. The maximum sensitivity must be used. Placing the sample next to a scintillation counter provides suitable sensitivity. Precipitating the iodine from the plasma as silver iodide and employing an end window is useful for determination of small amounts of radioiodine. Several charts, diagrams and photographs are presented.—*Charles W. Cooley, M.D.*

Crispell, Kenneth R., Parson, William, and Sprinkle, Philip. A simplified technique for the diagnosis of hyperthyroidism, utilizing the one-hour uptake of orally administered I^{131}. *J. Clin. Endocrinol. & Metabol.*, Feb., 1953, *13*, 221–224.

The authors studied 182 fasting subjects, including 6 healthy volunteers, who were given 4 to 8 microcuries of radioactive iodine (I^{131}) orally, and another group of 43 subjects who were given 4 to 8 microcuries intravenously. The thyroid uptake was measured at one hour and again at twenty-four hours by means of a scintillation counter. Thirty-two patients considered to be hyperthyroid clinically, and substantiated by response to therapy, had one hour uptakes ranging from 20 to 50 per cent. Ninety-six, considered to be euthyroid clinically, had one hour uptakes ranging from 7 to 19 per cent. The twenty-four hour uptakes in the two groups ranged from 46 to 96 per cent and from 13 to 46 per cent respectively. Two patients, considered to be euthyroid clinically, had both elevated one and twenty-four

hour uptakes. One had a subtotal thyroidectomy and no pathological evidence of hyperthyroidism was found. The other is still under observation.

Six subjects with myxedema had one hour uptakes ranging from 4 to 11 per cent, compared with 7 to 19 per cent in the 96 euthyroid subjects, thus giving considerable overlap. The twenty-four hour uptakes ranged from 1 to 10 per cent in the myxedematous group, and from 13 to 46 per cent in the euthyroid group.

The group in which the radioactive iodine was administered intravenously gave comparable results with the group in which it was given orally.

It was concluded from the above that the thyroid uptake one hour after the oral administration of a tracer dose of iodine may be used to separate the hyperthyroid from the euthyroid state. The twenty-four hour study still must be used to separate the euthyroid from the hypothyroid state.—*Charles W. Cooley, M.D.*

Johns, M. W., Gregson, J. H., Foster, G. C., Jaimet, C. H., and Thode, H. G. Radioiodine 131 in the diagnosis of thyroid function. *Canad. M. A. J.*, Feb., 1953, *68*, 132–137.

The authors increased the sensitivity of their detection instruments and were able to reduce the diagnostic dose from 200 microcuries to as little as 0.5 microcuries for some tests and to 25 microcuries for all tests. Three separate measurements of thyroid function were made, the radioiodine uptake, the conversion rate, and finally regional counting for patients who had nodules in the gland.

The authors found the conversion ratio to be more accurate than the uptake studies. The conversion ratio is the ratio of the protein bound I^{131} in a sample of plasma to the total I^{131} content of the same quantity of plasma. The agreement between the uptake and the conversion ratio is relatively good. The two methods of diagnosis differed in 21 per cent of the total cases. Most of these cases showed hyperthyroidism on the basis of the conversion ratio and were normal as judged by the total pickup. In many cases where the conversion ratio and radioiodine pickup tests were in disagreement the patients had been on antithyroid drugs or Lugol's iodine. In these cases the thyroid was either blocked or saturated and a low radioiodine pickup, therefore, resulted. The conversion ratio, on the other hand, most often gave the correct diagnosis. The conversion ratio test has also given advance warning in many cases of a hyperthyroid condition before clinical symptoms were apparent. The conversion ratio test was almost 100 per cent reliable in the diagnosis of hyperthyroidism.

Diagnostic tests were done on over 500 patients. One hundred and fifty patients with hyperthyroidism were treated and cured, producing only 1 case of hypothyroidism and no failures. Twenty patients with carcinoma of the thyroid were investigated and 9 treated. Five patients with carcinoma of the thyroid gland which were completely hopeless were operated on, and are now well two years after therapy.—*Frank J. Rigos, M.D.*

Wollman, S. H. Analysis of radioiodine therapy of metastatic tumors of the thyroid gland in man. *J. Nat. Cancer Inst.*, Feb., 1953, *13*, 815–828.

Most metastatic thyroid tumors do not accumulate enough I^{131} to be destroyed. Attempts have been made to increase the ability of these tumors to collect I^{131} by removal of functional tissue, and by administration of thiouracil or thyrotrophin. An observed increase in I^{131} uptake by the tumor associated with any one of the above treatments has been interpreted as being due to a response of the tumor to endogenous or exogenous TSH (thyroid-stimulating hormone).

In this paper the author makes an analysis of the problems of radioiodine therapy of metastatic functional carcinomas of the thyroid gland in man. Studies on the mouse are included in the analysis of quantitative conditions under which one might hope for complete destruction of functional metastases. Observations on the mouse showed that with small values uptake per gram of functional tumors of a given line is constant, but with larger uptakes a gradual decrease occurs.

A calculation was made of the required uptake of I^{131} per gram of thyroid tumor tissue assuming that it is desirable to completely destroy a tumor with a single dose. The dose of I^{131} currently used in clinical practice was assumed to be either 100 or 250 millicuries. The required I^{131} concentration in the tumor was assumed to be either 100 or 300 microcuries per gram. It was found that the I^{131} uptake per gram of tumor varied from 1/6 to 1/44 that of the thyroid gland of a standard man. The dose of I^{131} used limits the maximum allowable weight of tumor to between 330 to 2,500 grams, although if one assumes only 30 per cent uptake these weights must be decreased by a factor of 3. Because of physical considerations the required uptake per gram must be increased for a small tumor (by as much as a factor of 10 for a tumor diameter of 110 microns).

Few tumors of the thyroid gland in man have been reported to have received the estimated required uptake per gram, hence it appears that complete destruction of functional metastatic thyroid tumors may be a rare event. This, of course, cannot be used as a criterion to determine whether or not to undertake therapy.—*Frank J. Rigos, M.D.*

Barclay, W. R., Ebert, R. H., Le Roy, G. V., Manthei, R. W., and Roth, L. J. Distribution and excretion of radioactive isoniazid in

tuberculous patients. *J.A.M.A.*, April 18, 1953, *151*, 1384–1388.

The distribution of isoniazid (isonicotinic acid hydrazide) in uninfected and infected tissues in 3 patients with varying forms of tuberculosis was studied by the radioactive tracer technique by the authors. They employed C^{14} labeled isoniazid, using single doses as high as 430 microcuries. In 1 of the individuals a second tracer dose was given so that the total combined dosage of radioactive carbon was 860 microcuries. This, employing a safety factor of approximately 10, fell within the dosage range now considered to be safe. The studies were conducted on 3 patients; 1 patient having active pulmonary tuberculosis, another tuberculous adenitis, and a third patient having a tuberculous pleural effusion.

It was determined that the drug and metabolites were largely excreted in the urine. As much as 92 per cent of this material was recovered from the urine in 1 patient within twenty-four hours. In the other 2 patients, 75 per cent was recovered within twenty-four hours. The feces contained less than 1 per cent, and minute amounts were found to be excreted in the form of carbon dioxide from the lungs.

Surgery was performed on all 3 patients within a few hours after the labeled isoniazid was given. It was determined that peak blood levels and plasma levels were reached at the end of the first hour. These levels ranged between 2.8 and 3.5 micrograms per milliliter of blood. Normal lung tissue and skin contained approximately 1.79 micrograms of isoniazid per gram of tissue. Normal muscle, fat and bone contained 1.5, 0.78, and 0.61 micrograms per gram of tissue respectively. It is interesting to note that the capsule of the tuberculous lesion contained 1.88 micrograms of isoniazid per gram of tissue, and that 1.04 micrograms per gram of tissue was found within the caseous material in the tuberculous lesion. Similar findings were noted in the capsule of the tuberculous lymph node and within the dense caseous material within tuberculous node. The pleural fluid in 1 patient was also found to contain 1.65 micrograms per cubic centimeter at two and a half hours.—*John P. Storaasli M.D.*

JOHANSSON, SVEN A. E., and SKANSE, BENGT. A photographic method of determining the distribution of radioactive material in vivo. *Acta radiol.*, April, 1953, *39*, 317–322.

Localization of radioactive isotopes within the body is an important problem. Measurements by a Geiger-Müller counter are tedious and time-consuming. Methods using the blackening of photographic plates require a high concentration of the radioactive isotope.

The authors modified previous photographic methods, which employ a lead plate with a large number of holes placed between the photographic plate and the radioactive source, by using a plate with many small holes. In this manner any given point on the plate is affected by radiation coming only from a source immediately superimposed and the distribution of the radioactive material appears as a coarse pattern of dots. To increase the sensitivity of the method, a crystal of thallium-activated sodium iodide is placed in front of the photographic plate, thus adding the effect of the light produced by the action of gamma radiation on the crystal. The intensity required to blacken the plate is approximately inversely proportional to the area of the holes. The area of the holes and the thickness of the lead plate together determine the solid angle of the holes. Different lead plates are used depending upon the energy and the intensity of the radiation and the required resolution power.

Model experiments demonstrated that this apparatus gives useful pictures for relatively low concentrations of radioactive material. In vivo studies with I^{131} showed a satisfactory image of the thyroid with an exposure time of sixty minutes after administration of 500 microcuries. A significant uptake of iodine was demonstrated in an area of bone metastasis from thyroid cancer.

It is suggested by the authors that the method can probably be used for quantitative or semiquantitative determinations of the concentration of the isotope in tissues by calibrating a small part of the photographic plate with the collimated radiation from a source of known strength.—*Leslie K. Sycamore, M.D.*

BAUER, FRANZ K., CASSEN, BENEDICT, YOUTCHEFF, ELSIE, and SHOOP, LUCILLE. Jet injection of radioisotopes; a clinical study comparing needle and jet injection of I_{131}, K_{42} and Na_{24}. *Am. J. M. Sc.*, April, 1953, *225*, 374–378.

A clinical study comparing the rate of absorption of various radioactive isotopes from subcutaneous tissues by needle injection (hypospray) is described by the authors. In their series, normal controls and patients with various clinical conditions, including hyperthyroidism, hypothyroidism, and cardiacs with and without decompensation, were studied. About 0.5 microcuries of carrier-free I^{131} in normal saline was administered by needle in one thigh and by jet injection in the other, 5 inches above the knee. The absorption rate was determined by counting directly over the area of injection, using a wide angle calcium tungstate scintillation counter. The count was plotted against time in minutes on semilogarithmic paper. A comparison of the disappearance rates of the two methods was obtained by comparing "half-times," that is, the number of minutes required for the initial count to decrease by one-half. The authors found that absorption by jet method was exponential and quite constant in the controls. Pro-

longed "half-times" were found in patients with myxedema and in cardiacs with congestive failure. The results obtained with needle injection were variable, sometimes not showing exponential disappearance and very frequently the "half-times" of disappearance was considerably longer than that of the corresponding jet injection test.

Potassium^{42} and sodium^{24} in similar amounts were given in some of the controls and patients and the results were identical to those in which I^{131} was used. —*John P. Storaasli, M.D.*

Cox, L. Woodrow, and Chalmers, T. A. The exchange of sodium between plasma and extracellular compartments in pregnant women as determined by Na^{24} tracer methods. *J. Obst. & Gynaec. Brit. Emp.*, April, 1953, *60*, 195–202.

The authors performed Na^{24} tracer studies in 23 pregnant women to determine the rate of disappearance of sodium from maternal plasma into extracellular compartments. Most of the studies were made at the time of delivery, which in 9 cases was spontaneous and in another 9 cases by cesarean section. Of the remaining 5 cases, 2 were studied at term before the onset of labor and 3 during early pregnancy while abdominal hysterotomy was done.

Briefly, the procedure was as follows: 10 ml. isotonic sodium chloride solution labeled with 50 microcuries of Na^{24} was injected into the antecubital vein. The needle was then washed through with saline and connected by means of a three-way tap to a slowly operating drip infusion apparatus, which permitted the vein to be kept open. At intervals of from one to five minutes, blood samples were withdrawn and the radioactivity of the plasma was measured with the aid of an M6 liquid Geiger-Müller counter. The results were plotted as counts/ml. plasma with respect to time.

The authors give a concise description of the details of injection, of the preparation of the plasma, of the estimation of the radioactivity and of the corrections made for background. By making certain reservations and taking some precautions, no corrections were thought necessary for the excretion of the Na^{24} through the urine or sweat. It was calculated that the radiation dose to the mother was less than 0.1 r per day and to the fetus, if he remained in situ, was the equivalent of 0.05 r per day, both values being lower than the permissible daily tolerance dose.

The measurements demonstrated that the plasma concentration curves plotted against time can be analyzed into at least two exponential components, the first or fast component having a half-life of 60 to 70 seconds, and the second or slow component ranging from 6 to 10 minutes.

Equations are given (1) for relating the coefficients of these two components, (2) for expressing the percentage of total sodium in the interstitial fluid, (3) for expressing the percentage of plasma sodium diffusing out of the vascular bed per minute, and (4) for expressing the percentage of the total interstitial fluid sodium diffusing into the vascular bed per minute. The "sodium space" was calculated from the plasma radioactivity at equilibrium, knowing the quantity of Na^{24} injected into the blood stream. The coefficients, the absolute values involved in equations (2), (3) and (4), and the sodium space values for all cases are tabularly summarized.

In interpreting these values the authors believe that immediately after the injection all the Na^{24} is contained in the maternal plasma. Then the Na^{24} diffuses out of the plasma into different fluid compartments of the body. In animals it was observed that the "fast" component corresponds to diffusion into the muscle, liver, intestine and kidney, whereas the "slow" component is the result of diffusion into the brain, nerves and bones. In pregnant women the "fast" rate of diffusion out of the plasma is within normal range but the "slow" rate of diffusion is slightly increased due to the increased extracellular space. The authors pursued their studies for a period of only one hour, but longer studies by other workers revealed the presence of a third component which may be due to transfer of Na^{24} to the intracellular spaces or perhaps to absorption of Na^{24} by the bone. —*T. Leucutia, M.D.*

Cox, L. Woodrow, and Chalmers, T. A. The transfer of sodium across the human placenta determined by Na^{24} tracer methods. *J. Obst. & Gynaec. Brit. Emp.*, April, 1953, *60*, 203–213.

This article, which is the second in the series, deals with Na^{24} tracer studies of the transfer of sodium from maternal plasma to fetal plasma and vice versa. The studies were carried out in 20 pregnant women, 3 of whom had nonviable fetuses and were delivered by abdominal hysterotomy, 9 were delivered by cesarean section, 2 were delivered with forceps and 6 were delivered spontaneously.

In a manner similar to that described in the previous article, 10 ml. isotonic sodium chloride solution labeled with 50 microcuries of Na^{24} was injected intravenously shortly before the time of delivery. At intervals of from one to five minutes blood samples were withdrawn from the mother and collected until several minutes after delivery of the fetus and placenta. In the cases of nonviable pregnancy, samples of amniotic fluid and cord blood were obtained and in addition one portion of fetus and one of placenta were analyzed by using supernatant fluid, wet ash incineration and dry ash incineration specimens. In the other cases delivered at term only samples of amniotic fluid (except when the membranes were already ruptured), cord blood and placental blood were taken. In a few instances a sample of infant blood

was also obtained from the fontanelle or from the external jugular vein one hour after delivery. The radioactivity was measured and the results plotted as already described in the previous article.

The authors include two tables. The first table summarizes the pertinent data in the 3 cases with nonviable fetuses and the second table in the remaining 17 cases. They also give several graphs showing the chemically determined percentage of sodium in the fetus at varying gestation periods (as found in the literature), the plasma Na^{24} concentrations in the fetus, the sodium space of fetuses plotted against time allowed for equilibration, the transfer of sodium across the human placenta and the rate of transfer of Na^{24} across the human placenta.

The general conclusion is reached that the quantities of sodium transferred from the mother to the fetus are on an average 450 times greater than are needed for the growth increase of the fetus at the particular gestation period.—*T. Leucutia, M.D.*

Cox, L. WOODROW, and CHALMERS, T. A. The effect of pre-eclamptic toxaemia on the exchange of sodium in the body and the transfer of sodium across the placenta, measured by Na^{24} tracer methods. *J. Obst. & Gynaec. Brit. Emp.*, April, 1953, *60*, 214–221.

In the third article, the authors report the results of their studies with Na^{24} tracer methods on the exchange of sodium in the body and the rate of transfer of sodium across the placenta in case of pre-eclamptic toxemia. The three groups of patients used for this purpose were distributed as follows: (1) 19 of the 20 patients mentioned in the second article served as normal controls; (2) 20 patients had pre-eclamptic toxemia and of these 9 were delivered by cesarean section, 8 spontaneously and 3 with forceps; and (3) 8 patients had other types of complications such as hydramnios in 3 cases, normal third stage of labor in 2 cases and early termination of the pregnancy by abdominal hysterotomy in 3 cases.

As in the studies already described, 10 ml. isotonic sodium chloride solution labeled with 50 microcuries of Na^{24} was injected intravenously to the mother shortly before delivery. The maternal and fetal plasma concentrations of the Na^{24} were measured and plotted against time and then the quantity of Na^{24} transferred across the placenta was calculated. The details of the procedure were the same as recorded in the previous articles.

The results, together with all pertinent data, are summarized in three tables. Graphs are also given showing the average plasma concentration curves for the 3 groups of cases, the sodium space in per cent body weight in normal pregnancy and pre-eclamptic toxemia, the transfer of sodium across the human placenta and the rate of transfer of Na^{24} across the human placenta.

These results demonstrate: (1) that anomalous plasma concentration curves are observed in some of the toxemic cases; (2) that a diminished rate of Na^{24} transfer across the placenta occurs with anomalous plasma concentration; and (3) that all patients with recurrent toxemia have a diminished transfer of sodium across the placenta.—*T. Leucutia, M.D.*

Cox, L. WOODROW, and CHALMERS, T. A. The transfer of sodium to the amniotic fluid in normal and abnormal cases, determined by Na^{24} tracer methods. *J. Obst. & Gynaec. Brit. Emp.*, April, 1953, *60*, 222–225.

In the fourth article the authors give an account of the Na^{24} tracer studies made to determine the quantities of sodium transferred to the amniotic fluid in cases of normal pregnancy and in cases of hydramnios. These studies were performed as part of the experiments already mentioned. The list of patients included 9 cases of normal pregnancy when the fetus was delivered by cesarean section, 2 cases of normal pregnancy when a nonviable fetus was delivered by hysterotomy and 3 cases of hydramnios.

In the 11 cases of normal pregnancy, the Na^{24} tracer substance was injected intravenously just before performing the cesarean section or the hysterotomy. In the 3 cases of hydramnios, the amniotic cavity was tapped and the fluid was allowed to drip slowly away, then the isotonic sodium chloride labeled with 50 microcuries Na^{24} was injected intravenously and samples of fluid taken at intervals. Otherwise the assay for radioactivity was as already described.

The results of the single measurements in the 11 normal cases and of the serial measurements in the 3 abnormal cases are tabulated.

The following are the authors' findings: (1) Na^{24} appears in the amniotic fluid within six minutes of its intravenous injection in the mother; (2) in normal cases an equilibrium between Na^{24} in maternal plasma and the amniotic fluid is reached in about 5.2 hours, whereas in hydramnios the transfer occurs at a slower rate, equilibration being observed in about 36 hours; (3) the percentage of sodium in the amniotic fluid exchanged every hour is 19.1 in the cases of normal pregnancy and 2.8 in the cases of hydramnios; however, (4) since the quantity of amniotic fluid into which the transfer takes place varies considerably in hydramnios, the total quantity of the sodium exchanged per hour is of the same order of magnitude in the cases of normal pregnancy at term and in the cases of hydramnios.—*T. Leucutia, M.D.*

Cox, L. WOODROW, and CHALMERS, T. A. The transfer of sodium to the placental blood during the third stage of labour determined by Na^{24} tracer methods. *J. Obst. & Gynaec. Brit. Emp.*, April, 1953, *60*, 226–229.

In the fifth and last article of the series, the authors relate their experiments performed with the

aim of determining by means of Na^{24} tracer methods whether or not the transfer of sodium continues across the placenta after delivery of the fetus. These studies were carried out in 39 pregnant women, of whom 17 were delivered by cesarean section, 6 with forceps and 16 spontaneously. Twenty patients suffered from pre-eclamptic toxemia, 9 being delivered by cesarean section, 4 with forceps and 7 spontaneously.

In 36 women a tracer dose of Na^{24} was injected intravenously just before the time of delivery and blood samples were taken from an isolated segment of the cord, which was clamped off immediately after delivery of the fetus, and from a large vein of the placenta after it was expelled. In 3 women the Na^{24} was injected after delivery of the fetus and the blood samples were collected in the same manner. In all cases serial samples of the maternal blood were also taken. The details of the injection of the tracer substance, of the separation of the plasma, of the radioactive measurements and of the plotting of the plasma concentration curves against time were identical with those described in the previous papers.

The values obtained are set out in a table listing all 39 cases. A graph is also included displaying in 7 cases the changes which were observed in the fetal plasma concentration of Na^{24} during the third stage of labor.

It was determined that samples of placental blood taken at the end of the third stage of labor which in many of these cases lasted only one or two minutes showed a higher concentration of Na^{24} than samples of cord blood taken at delivery. In the 3 women in whom the injection was made during the third stage of labor, an appreciable quantity of Na^{24} was transferred to the placental blood. The authors, therefore, are of the opinion that an active uterine circulation persists for the first few minutes of the third stage of labor.—*T. Leucutia, M.D.*

Botsford, Thomas W., Wheeler, H. Brownell, Newton, Robert A., and Jaques, William E. Hypoplasia of bone marrow associated with radioactive colloidal gold therapy. *J.A.M.A.*, March 7, 1953, *151*, 788–791.

A total of 23 patients were treated with radioactive colloidal gold. An arbitrary division into two groups was made according to dosage: 1) those who received less than 50 mc. Au^{198} and, 2) those who received more than 50 mc. Au^{198}.

Eleven patients were given less than 50 mc., and in all of these the agent was administered interstitially. No side-effects or clinical evidence of bone marrow depression were ascertained in this group. Eight of these 11 patients died of their original malignant process and three were examined post mortem, all of whom exhibited normal bone marrow.

Twelve patients received 58–153 mc. Au^{198} on one or more occasions. Seven of these were intracavitary and 5 were interstitial administrations. Bone marrow specimens obtained at autopsy from 6 patients in this group revealed hypoplasia and particulate matter consistent with metallic gold (demonstrated by the method of Elftman and Elftman). Focal necrosis in the marrow was a frequent finding. Four of these 6 patients had received Au^{198} only and are reported in detail, while the other 2 had received triethylenemelamine and roentgen therapy in addition to Au^{198}. Focal areas of necrosis and gold particles were demonstrated in the marrow of one patient who expired only 72 hours following the intraperitoneal administration of radio-gold, indicating a rapid systemic uptake with bone marrow deposition. This has been observed by other investigators (Herve and Closon) who injected Au^{198} intraperitoneally in rabbits and demonstrated similar uptake and distribution to that obtained with intravenous injection. The authors describe, however, a patient with pseudomyxoma peritoneii who received 154 mc. Au^{198} intraperitoneally and who had a normal sternal marrow 2 months subsequently.

In clinical use, the bone marrow toxicity of Au^{198} should be remembered whether the substance be used interstitially or intracavitarily.—*Kenneth L. Krabbenhoft, M.D.*

Hale, William M., and Stoner, Richard D. The effect of cobalt-60 gamma radiation on passive immunity. *Yale J. Biol. & Med.*, April, 1953, *25*, 326–333.

In this interesting article the authors report the results of experiments devised to test the effect of whole body cobalt-60 gamma irradiation on the passive immunity of mice to pneumococcus, type III, tetanus toxin with specific antitoxin present at the time of irradiation, and the active immunity of influenza type A virus.

It was shown that whole body gamma irradiation with cobalt-60 in sublethal doses effectively destroyed the immunity to pneumococcus infection even with abundant specific antibody present. The authors believed that this destruction of the immunity was directly correlated with the drop on the leukocyte count. They were unable, however, to restore the resistance enjoyed by the nonirradiated animals either by the use of the whole blood transfusions or injection of fresh leukocytes.

In the experiments with tetanus toxin using neutral and 90 per cent neutral toxins no change was discernible in the group of irradiated mice and the unirradiated group.

In the experiment with influenza type A virus 700 rep of cobalt-60 gamma irradiation had no effect in depressing the active immunity once it had been established in these mice.

In both the tetanus toxoid and the influenza type A virus the presence of leukocytes is not necessary to

carry out the immunity. The authors feel this is the essential feature of these experiments.—*T. D. Allison, M.D.*

PARR, W., O'NEILL, T., and KREBS, A. A study of the x-irradiation protection afforded by cobalt. *Science*, Feb. 13, 1953, *117*, 155–156.

This study was undertaken to determine the influence of cobalt in total body irradiation effects. Approximately 400 female Swiss Albino mice were used for the experiment. They were divided into four groups as follows: group 1 on Purina stock chow diet; group 2 on cobalt diet; group 3 on Purina stock chow diet plus irradiation; and group 4 on cobalt diet plus irradiation. The mice were kept on these diets five and eight days before irradiation and for about fifteen days after irradiation. Food and water were given *ad lib.*

The animals kept on cobalt diet before irradiation showed a significant increase in their resistance against irradiation in comparison to the irradiated groups on Purina chow only. The general appearance of the cobalt-fed irradiated animals was quite similar to that of the nonirradiated animals. They exhibited smooth fur and normal vitality, whereas the irradiated animals on normal food and the few animals that died in the cobalt-fed irradiated group showed all the signs of heavy irradiation damage. The protective effect exhibited by cobalt is discussed and compared with present irradiation protection investigations.—*D. S. Kellogg, M.D.*

MISCELLANEOUS

MOELLER, DADE W., TERRILL, JAMES G., JR., and INGRAHAM, SAMUEL C., II. Radiation exposure in the United States. *Pub. Health Rep.*, Jan., 1953, *68*, 57–65.

The authors are engineers and research workers connected with the United States Public Health Service. They point out that members of the human race are always exposed to some ionizing radiations of cosmic origin and also from natural sources in the environment and within the body. They calculate that during a lifetime the average person who lives to be seventy years of age is exposed to about 9 roentgens of radiation from natural sources.

It is stated, however, that in modern days, additional radiation is absorbed from other sources such as radiation-generating machines, radioactive materials, medical roentgenography, radiation therapy, nuclear reactors and isotopes. The authors calculate that the total average annual radiation absorbed by human beings is about 2 roentgens, although certain segments of the population receive total exposures which approach the permissible upper limits of tolerance. This public health problem which at present is minimal in certain areas will probably become more widespread.

The present paper which includes calculations of exposure, grafts and charts as well as a good bibliography dealing with hazards will serve as a baseline for future studies when nuclear reactors will be used for power production, research, transportation and other diversified purposes.—*C. L. Hinkel, M.D.*

JAEGER, ROBERT. Die Standard-Dosimetrie ionisierender Strahlung und ihre Aufgaben. (Standard dosimetry of ionizing radiation.) *Strahlentherapie*, 1953, *89*, 481–516.

Equipment and arrangements for the absolute measurement of the roentgen were destroyed in Germany during the war. Through the cooperation of the Hessian Ministry of Culture, the Max Planck Institute for Biophysics in Frankfort am Main-Ockstadt, and numerous workers (particularly Prof. B. Rajewsky, who wrote the foreword to this paper, and Dr. R. Jaeger) the absolute physical measurement of the roentgen is again possible at the Max Planck Institute. Further, the small doses of radiation concerned in assessing radiation protection, of the magnitude of "permissible" daily doses, have been measured absolutely for the first time.—*Henry G. Moehring, M.D.*

HEDENBERG, I., ENGFELDT, B., and ENGSTRÖM, A. X-ray absorption and diffraction studies on experimental vesical calculi. *Brit. J. Urol.*, March, 1953, *25*, 33–37.

Bladder calculi were produced experimentally in albino rats and microradiographs were made of sections of these stones. In addition, several calculi from human patients were treated similarly. Stones with high mineral content absorbed roentgen rays readily and resulted in diffraction while those consisting mainly of organic material did not produce these effects. Both types were found in both groups suggesting that infection and stasis might be part of a common genesis for the production of these stones.—*C. R. McIntire, M.D.*